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SUMMARY

The inspection of this large generic OTC/Rx Drug Manufacturer and Medical Device Repacker was conducted per FACTS assignments #680105. Pre-approval assignment covered ANDA (b) (4) Cetirizine 5mg and 10mg tablets. The drug manufacturing portion of this inspection was conducted under CP 7356.002 "DRUG MANUFACTURING INSPECTIONS", 7352.832 "PRE-APPROVAL INSPECTIONS/INVESTIGATIONS", 7356.021 "DRUG QUALITY REPORTING SYSTEM – DQRS NDA-FIELD ALERT REPORTING"; and 7353.001 "ENFORCEMENT OF THE POSTMARKETING ADVERSE DRUG EXPERIENCE REPORTING REGULATIONS". The medical device repackaging portion of this inspection was conducted under CP 7382.845 Medical Device Manufacturers. Registration was verified during the inspection.

In early November 2006, the L. Perrigo Company ("Perrigo") notified the FDA of metal contamination findings in Acetaminophen, 500mg caplets and the decision to recall all lots manufactured from material supplied by a particular vendor. As a result, a directed inspection in conjunction with a planned GMP inspection was initiated 11/07/06.

Systems covered during this inspection include: Quality, Manufacturing, Packaging, Production, Facilities and Equipment, and Laboratory Systems. In addition a QSIT inspection of the Class II Medical device repackaging operations was conducted. Along with the above mentioned metal contamination of APAP (recall (b) (4)), follow-up coverage was given to several more of the recalls initiated in the past year including numbers: (b) (4) . Two DQRS complaints ((b) (4)) were also followed up (Attachments 3 & 4).

The current inspection revealed the following GMP deficiencies: Lack of complete investigation conclusion and follow-up and lack of thorough review of an unexplained discrepancy; quality control unit responsibilities not in writing or fully followed; failure to visually examine reserve samples; failure to apply results of stability testing in determination of expiration dates; lack of written procedures for the cleaning and maintenance of certain equipment; written production and control procedures not fully followed; Equipment not of appropriate design; deviations from written production and control procedures not justified; incomplete training given; written stability testing program not followed; established sampling plans not followed; entries in equipment logs not in chronological order; record of major equipment maintenance not included in individual equipment logs; failure to clean certain equipment and utensils at appropriate intervals; incomplete batch production and control records; representative samples of each shipment of each lot of component for testing not obtained; and complaint records lacked known reply to complainants in cases cited.

Management offered immediate corrective actions to many of the observations and written responses for the remainder.

Documentary Sample (b) (4) was collected during this inspection along with ANDA (b) (4), Profile Sample (b) (4) for Cetirizine 5mg and 10mg tablets.

ADMINISTRATIVE DATA

Inspected firm:	L. Perrigo Company
Location:	515 Eastern Ave. Allegan, MI 49010
Phone:	269-673-8451
FAX:	
Mailing address:	515 Eastern Avenue Allegan, MI 49010

Dates of inspection:	11/7/2006, 11/8/2006, 11/9/2006, 11/13/06, 11/14/06, 11/15/06, 11/16/06, 11/17/06, 11/20/06, 11/27/06, 11/28/06, 11/29/06, 11/30/06, 12/5/06, 12/6/06, 12/7/06, 12/15/06
Days in the facility:	17
Participants:	Patsy J Domingo, Investigator Rebecca E. Dombrowski, Investigator Martha Sullivan-Myrick, Investigator

The inspection of the firm commenced 11/07/06 first by Martha Sullivan-Myrick, Investigator joined later that same day by Investigator Rebecca E. Dombrowski.

Inv. Sullivan-Myrick initiated the inspection and presented official credentials and prepared FDA 482, Notice of Inspection to (b) (6), Associate Director Quality Assurance.

Inv. Dombrowski presented official Credentials and a prepared FDA 482, Notice of Inspection with attachment to Dr. Eric Kolodziej, Sr. VP Quality and Compliance and most responsible available at the time of issuance.

On 11/13/06, Investigator Patsy J. Domingo joined the inspection team, presented credentials and FDA 482 also to Dr. Eric Kolodziej.

At the close of the inspection, an FDA 483, List of Inspectional Observations was presented to Mr. John T. Hendrickson, most responsible in the absence of President/CEO, Mr. Joseph Papa.

HISTORY

No changes to the history of the firm were reported from the previous inspection. As before, this publicly owned company, incorporated in 3/23/88, was originally founded in 1887 by Luther Perrigo, and remains the largest manufacturer of over-the-counter pharmaceuticals for store-brand markets in the country. The firm's corporate headquarters are located at 515 Eastern Ave., Allegan, MI 49010, with US manufacturing plants within Michigan at Allegan and Holland in addition to Greenville, SC.

The recent sale of the (b) (4) was reported during the inspection, to be effective the end of December 2006. The new owners will continue manufacturing the effervescent products. Suppository production will be moved to Perrigo's New York facility.

Inspection History

Inspectional history dated to 4/26-7/14/00 is described in detail in the 8-9/2004 Establishment Inspection Report.

Since the August/September 2004 GMP inspection, this firm has been inspected for cause on two occasions: 7/2005 and 3/2006. The 7/2005 inspection resulted in the issuance of an 8 point FDA-483 regarding complaint handling and investigations while the 3/28/2006 inspection resulted in the

issuance of a 3 point FDA-483 regarding complaint handling. The 7/2005 inspection lead to the recall of several OTC drug products (b) (4)) manufactured for use by children.

In total, (b) (4) recalls have been initiated since 1/2005. Attached as Exhibits Pjd-590/593 is a listing of the recalls for calendar years 2005 and 2006. See Recalls section of this report for a description of those covered during this inspection.

FMD-145

Correspondence and post inspection FMD-145 letter should be addressed to:
Joseph C. Papa, President and CEO
L. Perrigo Company
515 Eastern Ave.
Allegan, MI 49010-1327

INTERSTATE COMMERCE/ JURISDICTION

The L. Perrigo Company continues to operate as a large scale generic drug manufacturer of both OTC and Rx products. The firm is also involved in the repackaging of a pregnancy test kit device.
The following lists and labels were collected as documentation of Perrigo's current product line:

1. Active Formula List (**Exhibit Pjd-594/602**) which includes the material # assigned, name, indication whether an ANDA exists (Yes or No) and the manufacturing status (Active, Development, About to be Discontinued, or Discontinued)
2. Projects Launched FY06 (**Exhibit Pjd-603**) which includes the product #, descriptive name, drug category, and date launched for new products since 9/2004
3. Approved Purchased Product List (**Exhibit Pjd-604/605**) which is a listing of Name and the number assigned to products packaged at this location or received as finished goods and distributed.
4. Tablet ID List (**Exhibit Pjd-606/612**) which contains the (b) (4) "FM" (product) number, the imprint (logo) and the product name.
5. Labeling (Rx) for prescription strength Naproxen Tablets (250mg, 375mg and 500 mg); Ibuprofen Tablets (400mg, 600mg, and 800mg); and Ibuprofen Suspension (100mg/5ml) (**Exhibits Pjd-659/676**).

The majority of all sales and distribution both to the firm and from the firm are from/to Interstate sources. Additionally, the firm operates as a Foreign Trade Zone for the importation of materials from (b) (4) to be further processed (Acetaminophen, Aspirin and Ibuprofen).
DOC Sample (b) (4) provides evidence of Interstate Shipment by the firm.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

The chain of command at the firm remains largely as reported during the latter inspection with certain significant changes. Specifically, Joseph C. Papa now resides as President and CEO of the firm, and is ultimately most responsible for the L. Perrigo Company. Also new to the management staff of Perrigo, is Dr. Louis W. Yu, Senior Vice President – Global Quality & Compliance. Dr. Yu is the most responsible for Quality Operations at the firm. John T. Hendrickson resides as second most responsible at the firm, titled Executive Vice President & General Manager, Perrigo Consumer Healthcare. Mr. Hendrickson received and accepted the FDA 483, List of Inspectional Observations at the close of the inspection in the absence of Mr. Papa. Dr. Eric W. Kolodziej, Vice President of Quality & Compliance reports directly to Dr. Louis Yu. Dr. Eric W. Kolodziej (Dr. Kolodziej) was our primary contact during the inspection, and accompanied us in all daily inspection activities. Daily information meetings occurred with Dr. Kolodziej.

A chain of command was collected and further details managerial hierarchy within the firm (**Exhibit # RED 1**-7).

Additionally, the following was verbally relayed detailing reporting structures and meeting schedules at Perrigo:

A "QURT" -Quality Unit Review Team meets weekly to discuss quality items and as needed with for cause concerns. This team consists of Dr. Kolodziej, (b) (6), and Ms. Renee M. Robbins, Senior Quality Assurance Manager. Additionally, a Product Safety Committee consisting of all Senior Executives in Operations, Supply Chain Management, Legal, Technical Division, along with Quality also meet as needed to discuss Marketed product issues.

Within other divisions of the firm, meetings occur per routine schedules as well. For example, the Technical Operations team, involved in investigations, meets each (b) (4) to discuss any and all deviations. Each morning, Quality Engineers and CIEs (Continuous Improvement Engineers) meet to discuss any new findings. At this time, any new investigations are discussed and assigned. This team is also involved in final approval of ongoing investigations.

The Quality Engineer team reports directly to (b) (6), who in turn reports to Dr. Kolodziej. All new information is shared as uncovered between (b) (4) statuses meetings held each (b) (4).

Additionally, all entered and initiated E-Notifications (Deviation Investigations) are, per default settings, shared with members of the Investigations teams and Quality. A complete list of the Perrigo associates receiving emailed e-notifications is provided as **Exhibit # RED 7**.

Technical Operations also compiles an updatable list of all deviations on a shared Perrigo Server, and adds to the status of ongoing investigations as new information is obtained. This list (view only mode for others) is accessible to Perrigo employees. As part of routine operations, the Quality Department reportedly reviews this list (b) (4)

According to Dr. Kolodziej, monthly Quality Counsel Meetings are also scheduled, with members consisting of the Executive Management Branch (Mr. John Hendrickson, and each department head). Discussions include any open deviations and meeting minutes are recorded.

Mr. Joseph Papa, CEO is made aware of deviation investigations at the time of Quality Counsel Meetings through Mr. John Hendrickson or Dr. Yu.

Subject matter experts and contacts addressed during the inspection include:

(b) (6), Associate Director Quality Assurance
(b) (4), Associate Director Quality Assurance
(b) (4) Associate Director, Technical Support
Bart D. Schrode, QA Manager Consumer Affairs
Jerry C. Pando, PhD, Director of Quality Control
Jeffrey Laws, Quality Control Senior Manager
(b) (4), Associate Director, Analytical R & D
(b) (4), R.PH, Associate Director, New Product Development
Kareena Parris, Quality Control Manager
(b) (4) Sr. QC Chemist
David Schrage, Director of Manufacturing
Steve W. Laninga, Tablet Manufacturing Manager
Amy L. Nunberger, Validation Manager
(b) (4), Associate Director, Validation
John Nadelin, QA Manager Consumer Affairs
Mike Reske, Manager Quality Engineering
Marta Williams, QC Stability Manager
John D. Brown, Manager Technical Operations
(b) (4), Packaging Engineer
Erika Ballman, Change Control Manager
Roger Reimink, Director of Distribution
Steve W. Laninga, Tablet Manufacturing Manager
Carla Krause, Document Control Manager
(b) (4), Vendor Coordinator/Film Coach
Mary Hildebrand, Art Director
Jennifer J. Ward, Records and Information Manager
Mike Andrus, Packaging Manager
Brain Hoffman, Transportation Manager

FIRM'S TRAINING PROGRAM
(MSM)
The firm's training procedure does not include retraining of personnel when a deviation investigation is classified as a Level I investigation. Level II investigations require manpower to be investigated and if the determination is made that the root cause is manpower, the firm retrains the individuals and documents this training. Observation 11 deals with the problems that can potentially arise with this plan of action.

MANUFACTURING/DESIGN OPERATIONS
(MSM)
Design changes have been made to both the tablet manufacturing and packaging areas. A Foreign Tablet Prevention Action list (**EXHIBIT MSM150-154**) was provided.

According to Mike Andrus, Packaging Manager, changes to the packaging line include; redesign the fillers, slated shelves for the tablets, covered recess fillers, remade hoppers, wires are no longer bundled, doors are no longer (b) (4), redesigned dryers, bulk lifter redesign, no longer use compressed air to clean but rather use vacuum, retraining employees in the importance of zero tolerance for tablets on the floor, separation walls between lines, hired QA technicians, and conduct investigations for all foreign tablets found.

According to Steve Laninga, Tablet Manufacturing Manager, changes to the manufacturing line include: return drums are all inverted with the lids off. Drums are not stored with liners in them, reduce operator movement between suites, dedicated cleaning group, zero tolerance for tablets on the floor, substandard box in each suite that is compacted after final yield (including box), dedicated employees for skid washing, and redesigning of uniforms to include knit cuff. This change was brought on, so as to eliminate the possibility of tablets from resting in the old uniforms with button cuffs.

TEMPORARY CHANGES
(MSM)

A list of temporary changes for suspensions (**EXHIBIT MSM-6**) was obtained. The firm uses temporary changes as a "quick" fix to their procedures. In some instances the temporary change is used for a short time. For example, a temporary change in a raw material supplier. In other instances, the temporary change will be in effect once the formal documentation control process and procedure review is complete. SOP (b) (4) (**EXHIBIT MSM7-14**) was in effect from 10/27/2005 until 06/29/2006 when the new revision (b) (4) (**EXHIBIT MSM15-22**) went into effect. Changes to the SOP are included on the revision list (**EXHIBIT MSM23**) and include a new step

for subsequent reviews, separate QA administrator duties from QA Technical Reviewer, and add detail QA Technical Review. Temporary changes are numbered with (b) (4) followed by a (b) (4) . After this number is a decimal point which dictates the revision number (example 01 or 02). During the review of the temporary changes for (b) (4) , I encountered several temporary change requests that were for the same change and overlapped in time but had different numbers. Even though these temporary changes had the same language, not all of them were included or referenced in batch cards. (b) (4) (**EXHIBIT MSM24-26**) was started in 11/13/04 and ended 1/13/05 (b) (4) (**EXHIBIT MSM27**) was started in 2/10/05 and ended 04/10/05. (b) (4) (**EXHIBIT MSM28**) was effective from 12/13/04 to 02/13/05. (b) (4) had the exact same language as (b) (4) but had a different number and over lapped the effective dates of both. Management stated that they are unaware of why this would have happened and the temporary Changes SOP will be reviewed to determine if these issues would still be present with the implementation of SOP (b) (4) (**EXHIBIT MSM15-22**).

Quality System(Pjd/RED)

Our inspection of the Quality System included review of deviations, rejects, complaints, returns and Out of Specification (OOS) test results and investigations. In addition, review of the quality systems established to track and trend production processes (annual product reviews (APR)), investigations, stability and validation activities was performed.

As a result of our review, the following deficiencies were noted: written investigations of unexplained discrepancies do not always include conclusion and follow-up (FDA-483 Item 1); failure to thoroughly review unexplained discrepancies and failures (FDA-483 Item 2); investigation of a failure of a batch to meet specifications did not extend to other batches that may have been associated with the failure (FDA-483 Item 7); procedures applicable to the Quality Control Unit are not in writing or fully followed (FDA-483 Item 3); Reserve samples packaged in opaque containers are not opened during the "visual exam" for signs of deterioration (FDA-483 Item 4); assigned expiration dating not supported by stability data (FDA-483 Item 5); written stability testing program not followed (FDA-483 Item 12); representative samples are not taken of each lot of components for testing or examination (FDA-483 Item 18); Batch records do not include documented reasons the line was down for extended time periods (FDA-483 Item 17);

As referenced in the Summary section of this report, this inspection was initiated in part due to Perrigo's report of metal fragments found in finished lots of Acetaminophen Extra Strength, 500mg tablets, product (b) (4). As a result a large portion of this inspection focused on the investigation into the metal found. This is detailed in the following.

Metal Contamination Investigation (RED)

Perrigo manufactures Acetaminophen (APAP) Extra Strength caplets, 500 mg under product numbers (b) (4) (b) (4) supplied Direct Compress granulation, '(b) (4) and (b) (4) (b) (4) supplied Direct Compress granulation, '(b) (4) The only difference in these two processes is the supplier of the Direct Compress granulation (DC) material.

Inspectional findings pertaining to the metal contamination in the 500mg Acetaminophen caplets, as reported by Perrigo to the FDA, are summarized here. Attachments # 1 and 2 further describe findings as obtained during this inspection.

On 8/16/06, at the completion of compression of product (b) (4) batch (b) (4) the press operator noted damage to the bottom of the right side feeder base on press (b) (4). This observed damage resulted in an investigation under e-notification (deviation tracking number) (b) (4). A copy of this yet ongoing investigation is provided as **Exhibit # RED 8-105**, and represents the investigation that ultimately led to the recall of all (b) (4) finished lots. To clarify pertinent aspects of the deviation investigation, the following summarizes the manufacturing process for product (b) (4) Acetaminophen, 500mg caplets.

Product (b) (4) is manufactured from a purchased granulation of (b) (4) Acetaminophen, Direct Compress (DC) material. This raw material (Perrigo part/material number (b) (4) is supplied to the firm from (b) (4) It is received by Perrigo in (b) (4), each with a plastic lock drum seal. The receiving department observes the drums for damage and accepts the shipment. The material is then subject to incoming sampling with Certificate of Analysis verification. Sampled drums are then relocked with a Perrigo metal seal. Received materials approved for use post-incoming sampling and verification are issued to batches according to FIFO principles. A process flow for product (b) (4) (both (b) (4) and (b) (4) can be described as:

(b) (4)

There is no wire like screen in the process or sieving step prior to compression. The tote charging step is required to transfer the raw material from drums into a container designed to dock to the compression equipment. Additionally, no significant changes to the process have occurred as verified with the batch record change control history (**Exhibit #RED 106-111**).

Each batch of (b) (4) is manufactured from (b) (4) of material (b) (4) Acetaminophen Direct Compress granulation), i.e (b) (4) drums are dispensed for each batch. In manufacturing, the entire (b) (4) of the raw material is manually charged into large, (b) (4) totes, drum by drum, through a hopper designed with a (b) (4) A photo of this security screen is provided as **Exhibit # RED 763**. A total of (b) (4) are resultant. These totes are

then delivered to a room above the compression suites, where the totes are docked to a conduit to be gravity fed into the compression machine.

Compressed tablets are routinely checked for weight, thickness, friability, and appearance throughout the compression run. As the tablets are compressed, they are collected into new drums. Tablets (caplets) of product (b) (4) are further coated prior to packaging. The caplets are loaded into pans (total of (b) (4) required for each batch of product (b) (4) and coated with a clear coat material. These coated caplets can then be packaged.

The tote loading process was observed on 11/07/06 for product (b) (4) (Acetaminophen 500mg caplets- manufactured from a direct compress material supplied by (b) (4) in a process consistent with that of (b) (4) The security screen was verified to consist of a large, laser cut stainless steel grate, and the tote docking area above the compression suites was verified to be void of any sieves or wire like screens. The method of manually tipping the (b) (4) drums onto the hopper and security screen however, was observed resulting in forceful metal on metal contact at the hopper-tote interface. Production Manager Steve Laninga confirmed the hopper-tote interface was metal on metal (FDA 483 Observation # 9). In corrective action to this observation, a new hopper was designed and implemented consisting of a raised hopper with support legs on the outside of the tote preventing the observed metal on metal contact.

An equipment list detailing the metal of each product contact surface in the (b) (4) process flow is supplied as **Exhibit # RED 367**. From this list, all are detailed to be of Stainless Steel.

Perrigo's Investigation – Deviation # (b) (4) (Exhibit # RED 8-105)

As referenced above, the investigation was initiated 8/17/06 due to metal wear damage noted on a feeder base on one side of compression machine (b) (4) at the completion of compression operations for batch (b) (4) In further review, batch (b) (4) (portions of which were collected and are provided here as **Exhibit # RED 112-246**) was found to have been compressed on two compression machines, only one of which (equipment # (b) (4)) was noted with wear/damage.
An '(b) (4) " was requested and performed 8/20-23/06 for (b) (4) tablets (caplets) of (b) (4) APAP 500mg Caplets, batch (b) (4) (the half of the batch compressed on machine # (b) (4) noted with feeder damage [Exhibit #RED 247-260]). This metal detection order resulted in 15 tablets (caplets) rejected for metal and a total of (b) (4) of substandard waste. Further inquiry into the (b) (4) of substandard waste revealed the reason for the relatively large amount of waste could not be fully described (Discussion item RED # 2). As a result of this discussion item, future metal detection orders will require a detailed description of substandard waste, whether due to spill, equipment waste, or tablets rejected for metal.

The (b) (4) rejected tablets confirmed to contain metal and a composite sample of tablets were directed to the QC lab for further analysis on or about 8/23/06 (according to the metal detection completion date). The sample, however, was not analyzed until 9/12/06. The results of the lab analysis of the tablets revealed (b) (4) original tablets contained metal fragments ranging in length from (b) (4)

As a result, an investigation into the processes that could have potentially resulted in metal contamination in the product and the supplier (b) (4) was directed as part of the same initial investigation (# (b) (4) .

A time line detailing the events surrounding this investigation was also supplied and is included as **Exhibit #RED 278-281**. In it, the internal investigation is detailed commencing 9/17 through 9/26/06 to rule out manufacturing processes as cause of the metal fragment findings. On 10/05/06, Perrigo issued the vendor (b) (4) a Supplier Quality Issue form regarding the metal fragment findings. On 10/09/06, Perrigo, Allegan requested an investigation of (b) (4) to be performed by Perrigo, China. On 10/11/06, Perrigo China provided information that the metal wire found in the tablets (b) (4) " (**Exhibit #RED 278**). On 10/12/06, Perrigo, Allegan expanded the material hold to other batches of (b) (4) produced with material (b) (4) from (b) (4) that was also used in (b) (4) On 10/19/06, the material hold was extended to all other raw material batches of material (b) (4) in house and products produced from (b) (4) as a result of the continuing Perrigo, China inspection of (b) (4)

The result of the Perrigo, China inspection resulted in a further inspection by Perrigo, Allegan. On 10/25-11/01/06, representatives from Perrigo, Allegan visited (b) (4) China and conducted a second inspection. The results of the inspection are provided here as **Exhibit # RED 91-94**, included in the initial deviation (51000003052).

Resulting from the findings as here listed and concern that metal fragments may be throughout batch (b) (4) based on the (b) (4) Inspectional findings, the entire batch (b) (4) (including the second half of the batch that had been compressed on a different compression machine then where the feeder damage was noted) was metal checked commencing 10/25/06 (**Exhibit # RED 261-277**). This check resulted in an additional (b) (4) tablets rejected for metal.

The (b) (4) rejected tablets and composite sample were again directed to the QC lab for further analysis. Results of the analysis revealed (b) (4) of the original (b) (4) tablets contained observable metal ranging in length from (b) (4) . Photographs of the actual fragments isolated are provided as **Exhibit # RED 56-61**.

These findings in conjunction with the findings from the (b) (4) China audit by Perrigo prevented Perrigo from ascertaining exactly when metal contamination of the raw material occurred. In addition, Perrigo's contracted consultants, hired to assess the potential risks associated with ingestion of wire-like fragments, lead Perrigo to a decision to recall all lots of Acetaminophen

500mg caplets ((b) (4) manufactured with Raw material #(b) (4) APAP, DC supplied by (b) (4) China (see also risk assessment, **Exhibit # RED 282-285**).

As above, this decision to recall was based on the inability to pin point exactly when (b) (4) China could have contributed metal wire like fragments to the granulation, and the results of the Medical Risk Assessment and Evaluation performed by an outside party for Perrigo. **Exhibit #RED 282-285** is a copy of this risk assessment performed. Specifically as detailed in the Medical Risk Assessment and Evaluation, and as stated by Dr. Eric Kolodziej, VP Quality and Compliance, the larger, wire like fragments were thought to pose a potential threat if ingested in that they were more projectile in shape and could possibly result in perforations. The Recall Press Release was issued on 11/09/06.

Perrigo Investigation into Metal Fragment findings performed during the FDA Inspection:

1-Perrigo performed a metal detection order on a lot of (b) (4) (APAP 500mg caplets compressed from (b) (4) supplied APAP granulation for direct compression) on a recently manufactured lot ((b) (4)) in attempts to show that the process flow for (b) (4) manufactured at Perrigo (includes both AK and AI) does not (therefore did not) contribute metal fragments to the finished, compressed tablets. Metal fragments were isolated from rejected tablets, many of which were sent to (b) (4) for metal analysis. Copies of fragments isolated from rejected tablets are provided as **Exhibit # RED 286-291**. Dr. Kolodziej concluded that what was observed from the (b) (4) tablets was not uncommon in industry, and with installed metal detectors in place, these tablets would be rejected without a problem. He further stated that Perrigo had no intention of recalling (b) (4) lots based on the metal findings here noted. He added that to have a tolerance of absolutely no metal in products would be prohibitive to continued business should such limits be required. He again added that the purpose of the installed metal detectors is to prevent tablets embedded with metal from being distributed.

2-Perrigo designed a protocol to pass raw material (b) (4) ((b) (4) DC APAP), lot (b) (4) through an inline magnet. The procedure involved removing any fragments retained on the magnets during charging, and placement of such on a form for later inspection and analysis. This protocol was performed 11/2006 and resulted in the retention of various metal particles. These particles were measured and then photocopied (**Exhibit # RED 295-301 and 302**) for inclusion in the report.

Metal isolates from 1- and 2- above along with isolated fragments from a later lot of (b) (4) lot (b) (4) processed through the metal detector, were sent to (b) (4) for complete metal analysis.

A (b) (4) Final report on the findings of the isolates from the (b) (4) study (1-above) and the Raw Material (b) (4) (2-above) is provided as **Exhibit # RED 303-337**. In it, a correspondent from (b) (4) describes the analyses performed on the isolates, and the findings of each. Specifically, (b) (4) concludes that the fragments isolated from raw material (b) (4) ((b) (4) supplied APAP DC) were steel, (b) (4) of which were of a stainless steel grade and the last, a carbon steel. Findings from the (b) (4) isolates revealed (b) (4) were (b) (4) while the other

two isolates were "(b) (4)" and "(b) (4)" (**Exhibit # RED 305**).

(b) (4) report on the isolates from the (b) (4) compressed caplet metal detection run (lot (b) (4)) and resultant rejected tablet metal isolate analysis revealed the fragments contained high levels of Chromium which was not observed in the (b) (4) fragments. In addition, graphite was also confirmed as the composition of particle 9 of the samples.

The finalized report for the fragments isolated from this (b) (4) compressed tablet lot as part of the (b) (4) Investigation (lot (b) (4) – a lot chosen for sampling and analysis by (b) (4) due to the large size of fragments found) is provided in copy as **Exhibits # RED 355-358**. These exhibits also include photographs of the original particles from the raw material, (b) (4) and finished tablet, product (b) (4) submitted for analysis. Perrigo performed a summary review of the (b) (4) data and concluded, "(b) (4) (b) (4) (b) (4)" (**Exhibit # RED 359-360**).

3- Perrigo devised a sampling protocol (**Exhibit # RED 361-366**) to collect samples from each drum of the oldest in stock lot of (b) (4) APAP DC material (material (b) (4)). This protocol was also performed on raw material, material # (b) (4). The fragments isolated from this process were not sent to (b) (4) Associates, Inc. for metal analysis.
Perrigo has been using materia (b) (4) APAP, DC) since (b) (4) Pharmaceutical Co. became an approved supplier in 2004.

4-Perrigo performed an assessment of all production equipment used in the manufacture of (b) (4) (both AI and AK) and found all to be Stainless Steel (**Exhibit # RED 367**).

Retrospective review of metal particles and fragments in (b) (4) Acetaminophen 500mg caplets performed by Perrigo during the ongoing investigation into deviation # (b) (4)

During the inspection, a request to review all metal detector equipment log records was made for a 2 year period. Documents provided revealed a total of 5 previous records of for cause metal detection runs for product (b) (4) Acetaminophen 500mg caplets prior to processing of lot (b) (4) (Exhibit #RED 409-411). They are:

Lot (b) (4) 12/19/04
Lot (b) (4) 12/20/04
Lot (b) (4) 12/22/04
Lot (b) (4) 07/25/06
Lot (b) (4) 07/28/06

Each lot was processed through in place metal detection units for cause as a result of an investigation. Each also resulted in findings of wire-like metal fragments (though this fact was not realized until 11/2006 as part of the firm's investigation (b) (4))-FDA 483 Observation # 1). The following information details the findings from the investigations for (b) (4) lots here listed. A list of all deviations pertaining to metal contamination was also requested and is provided here as **Exhibit # RED 412-413**.

12/2004

I - On 12/13/04, Deviation Investigation (Perrigo Quality Notification) #(b) (4) was initiated for (b) (4) batch (b) (4) due to plenum and coating pan wear noted on pan 044 (**Exhibit #RED 414-476**, including related metal detection orders and results). The investigation expanded the affected batches to include all processed in the damaged coating pan since the time of the last major clean (last documented point in time when no damage was noted). This included batches (b) (4) (both (b) (4) products), and (b) (4) (both (b) (4) products).
100% metal detection of each of the affected batches was performed immediately (12/13-16/04) and resulted in the following:

Product	Lot	# Rejected tablets
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		
(b) (4)		

(b) (6). The manufacturing sequence of the above occurred in the order as listed, thus the increase in # of rejected tablets would not have been of interest (because the firm was not certain of exactly when the plenum wear commenced, they only knew the time of the last major clean when all equipment was found without damage). The increase in rejected tablets may have appeared to represent the time when the most damage had occurred to the plenum and drum – however, the increase was noted when lots switched from (b) (4) to (b) (4)

The rejected tablets were amassed and sent to Perrigo's QC laboratory for Special Sample Testing. Testing occurred 12/23-30/04 and revealed:

(b) (4) → particles ranging in size from (b) (4)
(b) (4) → particles ranging in size from (b) (4)
(b) (4) → particles ranging in size from (b) (4)

Each laboratory test result Certificate of Analysis was stamped "APPROVED" with a test result of "PASS" (Specification states "(b) (4) ") and signed and dated by a lab approving official (dated signatures from 12/23-12/30/04).

The deviation references the laboratory data and summarizes under the "Results of Investigation/Assignable Cause" section of the investigation, "(b) (4) " and under "Recommendations:", "(b) (4) " (**Exhibit # RED 420**). As here quoted, the results of the composite testing are summarized (true statement in that no metal fragments were found in the composite samples) but the conclusion does not include the results of the individual tablet analyses and metal fragments found here (i.e. the # of rejected tablets and QC analysis results of each individual rejected tablet). The investigation was signed and finalized 02/02/05 by Quality.

Laboratory procedures (b) (4) , Foreign Matter in Raw Material, Tablet Mixes, or Granulation, were reviewed. Each specifies that all foreign matter found through the tablet extraction process is to be placed in a bag and labeled. The bag is to be stapled to the batch documentation (**Exhibits #RED 477-482**). SOP (b) (4) (**Exhibit # RED 513-515**) further governs the flow of samples to the lab under special assay request as was explained by the lab management team to be the procedure in place for Metal detection sample requests.

In this deviation investigation ((b) (4)), no further review of the metal fragments found in the tablets rejected for metal was described and the fragments found were not related back to the original deviation (wear and scrapes on coating equipment to wire like fragments found in rejected tablets).

II - Deviation investigation # (b) (4) (**Exhibit #RED 483-489**) initiated 5/28/06 displays a similar pattern of investigation in that the deviation was initiated because a hex nut had been found by an operator during compression operations of (b) (4) lot (b) (4) and resulted in a metal detection order yielding (b) (4) tablets rejected for metal (though a (b) (4) was what had initiated the metal detection order). Portions of Batch (b) (4) were also copied and included as **Exhibit # RED 490-501**. **Exhibit # RED 502-512** is the metal detection order records for same. Laboratory analysis of the rejected tablets revealed wire like metal fragments of varying dimensions had been isolated. **Exhibits # RED 473** through **476** are photos of the isolated metal fragments from tablets rejected for metal in lot (b) (4) One of these fragments in particular measures greater than (b) (4) in coiled form (**Exhibit # RED 475**).

This deviation investigation was signed off as completed on 7/20/06, (b) (4) before the metal detection run had initiated (**Exhibit # RED** (b) (4) – for deviation sign off, **Exhibit # RED 502** for the initiation of the metal detection order for this same lot).

In Perrigo's investigation into deviation (b) (4) (the ongoing, current deviation resulting in the recall), a summary of this retrospective review as described here is detailed (**Exhibit # RED 13**). Perrigo concludes "The batches from deviations (b) (4) were to be reworked (metal checked) prior to packaging and the potential for metal in the product was determined to be present through the investigation. The metal check results from Quality Control testing were not reviewed by Technical Operations to determine if there was an additional source of metal". The failure to fully evaluate the findings from the lab analysis and metal detection process resulted in **FDA 483 Observation # 1**.

Additionally, as detailed under item I above, laboratory procedures (b) (4) , effective 4/12/01 ("(b) (4) " as stated in each respective procedure), require that all foreign matter found be saved, placed into a labeled bag, and stapled to batch documentation (**Exhibit # RED 479 and 482**). In discussions with (b) (6) regarding the retrospective review performed, he stated that the review and resultant photos obtained and provided (**Exhibits # RED 470-476**) were obtained by reviewing batch records of product (b) (4) lots involved in a metal sort process as part of and during the (b) (4) investigation.

To rule out the manufacturing process as a source of the metal observed in (b) (4) finished, compressed tablets from (b) (4) and the (b) (4) – DC Acetaminophen, raw material used in (b) (4) production were also reviewed by Perrigo. A log record listing of all metal detection runs performed 2004 to present, revealed a total of 3 previous runs for cause in 2005 and 2 in 2004 had been performed for Perrigo product (b) (4) (lots (b) (4)). A copy of the log records displaying the 2005 metal detection orders is provided as **Exhibit # RED 873-874**. Associated deviations and metal detection results from these runs were requested and reviewed during the current inspection.

Deviation investigation (b) (4) pertained to (b) (4) lot (b) (4), with notation of grey matter observed. The investigation related the matter observed to the press on which the batch was compressed and resulted in corrective actions and metal detection of the lot. The metal detection resulted in tablet rejects, only (b) (4) of which were confirmed metal, with sizes from (b) (4) in length.

Deviation investigation (b) (4) also pertained to product (b) (4) . The investigation revealed the feeder paddle to the feeder base had been incorrectly installed. Review of logs bracketed the affected batches. These batches were metal detected, revealing (b) (4) tablets from lot (b) (4) and (b) (4) from lot (b) (4) rejected for metal. No discrepancies were noted.

No problems were noted with either deviation investigation covering the for cause metal detection runs observed from the metal detection log review.

During the inspection, Perrigo had initiated the procedure to pass the raw, incoming bulk DC Acetaminophen granulation through in place/in line magnets at the tote loading stage of manufacture. From this process, fragments of metal (if any) can be captured and collected per procedure. The fragments collected from recent productions had been sent to (b) (4) for metal analysis. The results of these analyses by (b) (4) had not yet been received at inspection close-out.

Corrective Actions taken by Perrigo as a result of the Metal Investigation

Perrigo has performed extensive corrective actions in addition to the (b) (4), Acetaminophen recall as a result of the metal contamination findings in the supplied raw material. These include (some described above and re-listed here):

-Auditing the supplier of the granulation ((b) (4) China) – (**Exhibit # RED 91-94**)

-performing for cause metal detection of all yet in house lots of bulk packaged (b) (4) lots, with QC analysis of rejected tablets and isolation of metal fragments uncovered

-contracted an external consulting firm to perform risk assessment of the metal fragments found from the above for cause metal detections (**Exhibit # RED 282-285**).

-performed investigational metal detection of a bulk lot of (b) (4) to determine if metal contamination existed in these compressed tablets (the manufacturing process for (b) (4) is equivalent to (b) (4) including the same equipment), (**Exhibit # RED 286-291**).

-Devised a sampling protocol for an in house lot of the raw material granulation to determine the extent of the metal in the incoming raw material from (b) (4) China – (**Exhibit # RED 361-366**).

-Devised a protocol to pass a lot of raw material through an in-line magnet in attempts to further characterize and quantify metal in the DC granulation raw material (**Exhibit # RED 292-294**).

-Revised a manufacturing procedure to incorporate an in-line magnet at the granulation loading stage permanently (**Exhibit # RED 516-517**).

-isolated and retained any metal or particles found on the magnets from any processed (b) (4) lots of granulation (found on this newly implemented in-line magnet). Results from the first batch processed via the new procedure provided as **Exhibit # RED 518-519**.

-Remodeled the hopper-tote interface at the granulation loading stage to prevent any metal on metal contact.

-Sent samples of extracted metal from both (b) (4) metal rejected tablets and (b) (4) metal rejected tablets, along with fragments isolated from the (b) (4) granulation raw material sampling protocols and the (b) (4) in-line magnets, to a contracted laboratory for full metal analysis. (All results aside from those of the recent (b) (4) metal particle analysis extracted from the in-line magnets) had been obtained prior to inspectional closeout (photos from the recent (b) (4) production are provided as **Exhibit # RED 518-519**).

-Sent out a '(b) (4)' to all applicable suppliers (copy provided as **Exhibit # RED 520-521**).

In addition, Perrigo had already committed to the complete installation and activation of metal detectors on every compression system. This implementation is scheduled for completion by January 2007. A spreadsheet displaying the time lines for complete installation (including qualification, validation, and cleaning validation) is supplied as **Exhibit # RED 380-382**.

Perrigo has also installed an X-ray system on the packaging line which is currently in use and capable of detecting larger metal contaminants (such as a bolt or screw) in packaged products. This system was not further covered during this inspection.

As part of the system inspection coverage, Product (b) (4) Annual Product Review (APR) 2005-2006 was requested for review. Pertinent copies from this APR were selected and provided here (**Exhibit # RED 522-528**). Included in this is the summary of process related deviations. The deviation codes resultant over the year are detailed here. This list also shows the great number of codes available for selections, many of which appear similar and require further review of the deviation to determine the exact nature of the complaint. This concept of using numerous sub-groupings to classify deviations was discussed with management. Dr. Kolodziej and (b) (6) agreed a less granular approach may be warranted (see also FDA 483 Observation # 3).

No discrepancies were noted during the APR review.

Metal Detectors

Installation, Operation, and Process Qualification and Validation of the Metal Detectors currently in place was reviewed during this inspection.

(b) (4) (System Authorization Number) was reviewed for metal detector validation (EQ – Equipment Qualification) including (b) (4) recently purchased and installed detection units.

The (b) (4) Metal Detectors, Tablex MC Model, Validation report dated 10/27/06 was reviewed with executed protocol and data. The Validation included challenges to installation, operation and performance of the equipment. I compared the challenges performed to the specified parameters in the units' operating and instruction manual. Initially, certain set points were not included as part of the EQ packet, but upon questioning, the missing information was supplied. For example, the "Engineer Mode Settings" as supplied on the document provided as **Exhibit # RED 368-369**. Lisa McNeil of validation stated that these Engineering Specifications will be incorporated in future such EQs.

Other review questions raised included the rate of flow of tablets through the metal detectors selected to represent a full run. I asked if the number of tablets passing through the metal detectors as observed during a tour of the facility would impact the workability of the metal detection unit. In response, (b) (6) provided a letter directly from the metal detection unit supplier indicating the volume of tablets should not have an impact (**Exhibit # RED 370**).

According to the Operating Manual and EQ, the detector operates under use of a penetrating electromagnetic field, and is capable of detecting metal fragments (b) (4) in size. As metal fragments of the sizes listed are passed through the electromagnetic field, the field is distorted resulting in rejection of the tablet passing through the detector. The rejection mechanism is not tablet specific, but rather timed to ensure removal of the metal containing tablet from a moving conveyer belt, and thus other tablets alongside may also end up rejected. For this reason, the firm will pass all rejected tablets through the same electromagnetic field a second pass; those rejected a second time are confirmed rejects for metal contamination, and are counted as metal tablet rejects.

Summary conclusion for the protocol and executed qualification supported successful equipment validation for use of all (b) (4) units and find that's that the EQ protocol execution yielded acceptable results in all capacities (**Exhibit # RED 371-373**).

Certificates of Conformity for the calibration verification units used with the metal detectors were further reviewed. Data revealed the units were provided by the Manufacturer of the Metal Detection units for use with the detection units. Copies of all Certificates are provided as Exhibit # **RED 374-379**.

Many more metal detection units of the same make and model have also been purchased and are under qualification and validation at this time. Anticipated date of completion for full in service date is by January 2007. A timeline displaying current activities and future activities to be performed was provided by Mr. S. Laninga, Production Manager, a copy of which is included as **Exhibit # RED 380-382**.

Lastly, the current procedure for use and operation of the metal detectors was reviewed. A copy of the procedure, SOP (b) (4) was provided (**Exhibit # RED 383-408**).

Two discrepancies noted in the SOP included: lack of requirement for an end of run calibration challenge (Discussion item # RED 3), and lack of specificity pertaining to substandard waste generated during processing (Discussion item # RED 2). Each of the above discussion items were verified corrected within a week of observation with updated procedures in place for both an end of run challenge and clarification on all substandard waste.

In conclusion, Perrigo strongly upholds that the metal contamination of wire-like fragments initiated from the supplier and was not due to their facility, procedures, equipment, or other materials.

Materials System (RED)

The materials section was briefly covered during this inspection to include the incoming specifications and tolerance limit establishment for (b) (4) raw material # (b) (4) and coating materials used in coating solution preparation.

Additionally, the criteria used in accepting (b) (4) China supplied raw material APAP (b) (4) DC granulation, raw materia (b) (4) was also reviewed as part of the metal contamination investigation as detailed above.

SAP system remains in place for the tracking and control of all materials and products in the firm as reported during the previous inspection. Challenges to the Hold system in place to prevent the use of quarantined product were made in conjunction with the produc (b) (4) recall without discrepancy.

Changes to the system included the increased screening of Direct Compress granulations (for use in (b) (4) for metal using in line magnets, and a project profile initiated to address natural materials handled by the firm and potentially more susceptible to microbiological contamination (**Exhibit RED #742).**

During review of the coating process, equipment, and materials, protoco (b) (4) **Exhibit # RED 808-812** was reviewed pertaining to hold time studies and microbial bioburden. This protocol established that for a matrix of coating solution preparations, each could be held for at leas (b) (4) , however, was not based on a worst case scenario for the coating material as permitted per incoming material specifications (FDA 483 Observation # 8). In corrective action to this observation, and as part of an ongoing effort to reduce incoming raw material specifications for Aerobic Plate count bacteria, many coating material specifications have been reduced.

Facilities and Equipment System(Pjd/RED)

Our inspection of the Facilities and Equipment System included observation of the various manufacturing and packaging equipment during our tours of these processing areas; review of equipment cleaning and use logs, review of equipment cleaning validation and review of validation documentation associated with new equipment acquired since the 2004 inspection. New equipment acquired since the last inspection includes the (b) (4) washer and in-line tablet metal detectors being stalled in each tablet press suite. Observations associated with equipment include: FDA-483 Item # (b) (4) ., failure to establish cleaning and maintenance procedures for product transfer hoses; FDA-483 Item (b) (4) . use of the wrong cleaning procedure for the (b) (4) pre-mix tank; FDA-483 Item #9 equipment used in manufacture of APAP Capsules not of the appropriate design due to observed metal on metal contact at the hopper/tote interface used to charge ready to compress granulation; FDA-483 Item 15 failure to document equipment maintenance in the equipment use log; and FDA-483 Item 14 equipment cleaning and use logs are not in chronological order.

The Cleaning Validation Master Plan (**Exhibit # RED 529-544**), (b) (4) was also reviewed during this inspection. The plan provides an overview of the cleaning schematic in use at the firm and the generalized approach to cleaning. Specifically, the firm is using a (b) (4) approach to cleaning with a worst case product or products selected for each cleaning procedure. This worst case product (indicator product) is selected for each cleaning procedure based on the solubility of the active ingredient. In challenges performed (cleaning validation), the ability to effectively remove the indicator product will cover all remaining products used on the same equipment using that

particular cleaning procedure. Other procedures in place supporting the Master Plan include that for: (b) (4) . Discrepancies noted with the plan included a lack of hold time data to support equipment held in an unclean state for periods of time prior to cleaning. However, studies to address this deficit are currently underway, working retrospectively with prior validated equipment/products and concurrently for new equipment/products.

To further review the Cleaning Validation Master Plan, selected pieces of equipment were reviewed and are detailed as follows:

Cleaning validation of the newly installed (b) (4) washer for use in packaging slat filler cleaning operations was reviewed without incident. All evidence suggested the equipment could perform as designed. The objective of the slat washer is to reduce the potential tablet carryover in the slats between filling operations as part of the (b) (4) The (b) (4) data reviewed indicated that the intensity of the washing procedure and design of the wash system would reduce or eliminate this carryover in the fill slats.

The Equipment Qualification and protocol for the Tablet Metal detectors used in metal detection operations at the firm were reviewed and are discussed above under the Metal Contamination section of this report.

Equipment Qualification for the (b) (4)) was reviewed. The executed protocol included planned manipulations to (b) (4) , Solution flow rate, air inlet flow rate, atomizing air pressure, outlet air temperature, and inlet air temperature. All deviations noted during protocol performance were investigated, reviewed, and corrected. No review discrepancies were noted.

(b) (4) CLEANING VALIDATION (MSM)

According to Eric Kolodziej, the firm is in the process of cleaning validation for the (b) (4) mixers and the pre mix tanks used for products manufactured on the (b) (4) mixer (**EXHIBIT MSM-79**). The validation is to go from a semi automatic to a complete manual operation and also to change cleaning solutions to the (b) (4) This change in cleaning solutions was explained by Mr. Kolodziej as a way for the firm to reduce the amount of cleaning solutions the firm uses throughout their plant. The validation is being conducted by family of products. The (b) (4) suspension will be validated first and then the APAP product family. Three cleaning validation runs have been attempted. The first 11/20/06 failed, the second 11/21/06 was not finished, and the third on 11/26/06 was not released at the time of this inspection. The validation is being conducted under temporary change order (b) (4) (**EXHIBIT MSM74-76**).

Production System
Pjd/RED

Production system coverage was accomplished through the coverage of pre-approval product Cetirizine HCl and the investigation surrounding metal contamination of APAP Caplets (see those specific sections of this report).

As noted in the Cetirizine discussion, Perrigo's current practices, as described in SOP (b) (4) (**Exhibit RED-845/850**) is to allow (b) (4) from the date of manufacture of the previous stage (between mixing and compression for example) although the expiration dating assigned is based on the first day raw materials are mixed together. If the tablet requires coating the material will have an additional (b) (4) to the completion of coating. Once completed, the bulk tablet can remain in bulk packaging (usually poly-lined drums or boxes) for up to (b) (4) longer.

During my (Pjd) review of the rejection printouts, referred to by Quality Assurance as "RIDs" or "IDs", which listed all rejected materials organized by category/reason for the rejection, I noted several examples of in-process batch material listed as rejected and the reason listed had to do with exceeding the time limit. As noted in the Annual Product Reviews (APR's) reviewed during this inspection (see **Exhibit Pjd-405** for example) all such rejects are listed. I expressed my concern that the various types of rejects (b) (4) for 2004/2005 and (b) (4) for 2005/2006) are not delineated so as to assess rejects related to failed manufacturing process versus rejects resulting from failure to complete the manufacturing process within time limitations. Dr. Kolodziej noted my concern.

For bulk tablets received from another manufacturer, such as the case with 81 mg Aspirin manufactured by (b) (4) (product (b) (4) Perrigo allows up to 6 months from the date of receipt for final packaging to be accomplished. Although specific examples were not noted, I expressed concern that stability studies might not include the worst case hold times associated with bulk tablet storage times. See FDA-483 Item #5 which pertains to stability problems associated with product (b) (4)

Laboratory System (RED)
Sample receipt, tracking, analysis, and reporting were reviewed during this inspection for both the Quality Control – Chemistry laboratory and the Microbiological laboratory.
Procedure, SOP (b) (4) was followed during a tour of the chemistry lab without note. Lab analysts with Perrigo utilize a (b) (4) database system for sample tracking, entry, analysis, and reporting.

Lab data and results may be input into (b) (4) directly using the (b) (4) entry interface as the original data, or written into bound laboratory notebooks and secondarily transcribed into (b) (4). According to the above lab procedure, either may be used.

The lab equipment included numerous dissolution baths, HPLC systems and linked software programs, desicator storage units for reference standards, solution and reagent preparation stations, moisture analyzers and numerous (b) (4) portals. All equipment observed was calibrated to date, standards were clearly labeled and stored according to specifications, and reagents in date.

Equipment use and maintenance logs were challenged for certain pieces of equipment without note. Weight standards for balance verification checks were also observed calibrated and properly stored.

A discussion point was raised regarding the condition of the mechanical mortar and pestle used in tablet grinding operations. The equipment was observed un-cleaned, with a chipped bowl and damaged flange on 11/27/2006, during the laboratory tour (Discussion item RED # 4)

Microbiology Laboratory (RED)

A tour of the microbiological lab occurred on 11/30/2006 led by the Director of Quality Control, J. Pando and the Laboratory Manager John Glave, along with the Laboratory Supervisor. The tour followed the flow of samples through the lab. The same (b) (4) database is in play in the micro lab and samples are logged in upon physical arrival.

The Microbiology lab is located in Plant 1 of the facility, downtown Allegan, and is staffed by (b) (4) (b) (4) microbiologists. These microbiologists are divided into two groups: the validation group, and the Release testing group. Included in routine sample testing operations are water samples collected from various ports throughout the firm.

The lab is equipped with numerous Biological Safety Cabinets (HEPA filtered), Freezers tied to a generator, an autoclave (mapped and qualified using biological indicator spores species), a speciation –identification system, along with water baths, incubators, and refrigerators.

The firm has also recently acquired a new microbiological enumeration system, though it has not yet been qualified or validated for use.

One of the lab biological safety cabinet hoods was selected for review of qualification data. Smoke studies and classification recertification was reviewed without incident and all related instrumentation was found in tolerance. Each Biological safety cabinet-hood is rated class 100 capable with unidirectional airflow under dynamic conditions.

The lab both purchases and batches media used in incubation activities, and the water component is autoclaved prior to use (DI water sourced through firm). Growth promotion is performed on each lot of media manufactured serving as the positive control for subsequent growth activities.

Several pieces of new equipment have been added to the microbiological lab including (b) (4) Refrigerators, (b) (4) ultra low freezers, and (b) (4) incubator. A list of new equipment purchases was also provided (**Exhibit # RED 545**). These new equipment pieces have also yet to be validated for use. Also anticipated for the coming year is installation of a (b) (4) security system to monitor critical storage units, refrigerators, freezers, and incubators in the lab to ensure each is maintained between allowable limits at all times.

The autoclave used for media, tools, and waste cycles undergoes annual performance qualification studies including (b) (4) challenges along with weekly performance checks. An initial discrepancy with dates listed in the last Qualification was clarified during the review. No other discrepancies were noted, and all studies including heat penetration studies revealed passing results.

Listing of all confirmed laboratory Out of Specification findings (OOS list- **Exhibit # RED 851-853**) was reviewed, (b) (4) of which were further reviewed.

(b) (4) – was due failure to perform proper testing. The impacted (b) (4) is received as a finished product in bulk. Analysts did not perform micro testing as (b) (4) result was provided for this test. Later change in (b) (4) specification removed (b) (4) listing preventing recurrence. There was no reported product impact as the lot had been tested by the contract manufacturer and passed.

(b) (4) – The starting material did not meet defects criteria and was rejected before use (Contract Facility)

(b) (4)
(b) (4) --
(b) (4) --
(b) (4) --
notified.

Pertained to Incoming Material – Failure to meet specification (particle size - failure) and each lot of material was rejected before use and the supplier

(b) (4) --
(b) (4) --

(b) (4) – Material Failed Microbiological Testing – resulted in rejection of material.

(b) (4) – Material Failed Microbiological Testing - resulted in rejection of material.

No discrepancies were noted and all investigations were timely and complete.

Packaging and Labeling System (Pjd)

Our review of the Packaging and Labeling System included observation of packaging operations as conducted in Plant (b) (4) Numerous changes have been instituted in the Packaging department aimed at the reduction of Perrigo foreign tablets found in Perrigo product. Changes include: the addition of walls between the packaging lines; new uniforms for employees eliminating cuffs, and pockets above the waist; the purchase of the (b) (4) high temperature/high pressure washer for slat fillers and other removable parts of the packaging equipment; redesigned fillers, and eliminating the use of high pressure air hoses when cleaning packaging lines.

Despite the above mentioned improvements, a number of complaints have been received and deviations have been initiated for foreign tablets found in products manufactured and/or packaged by Perrigo or for foreign tablets found somewhere in the process (see Exhibit Pjd- 677/679 for the list). Several of these investigations were selected for review including:

Medical Device QSIT (MSM)

This inspection of a medical device repacker was conducted under (b) (4) . The firm is currently registered as a repacker/ relabeler of Class I and Class II medical devices. Class I devices include an instant Heat Wrap and Ovulation Predictor Test Kit. The Class II device is a Pregnancy Test Kit. The firm has been a repacker of the Pregnancy Test Kits since 1995. The Ovulation Test Kit and Heat Wrap have only been repacked since 2004.

The focus of this inspection was on the Pregnancy Test Kit, the firm's only Class II Medical Device. The Pregnancy Test Kit is developed and manufactured at (b) (4) . Perrigo entered into a signed contract with (b) (4) on 10/10/02. The first kits were received on 12/11/02. The devices are packed into flexible pouches. The specifications (**EXHIBIT MSM-78**) for materials and print, are determined by Perrigo with guidance by (b) (4) Perrigo has a written quality agreement with (b) (4) be notified of any changes made to raw materials. On site audits are conducted yearly at the (b) (4) assumes ultimate responsibility for the finished devices.

The pouches are then sent to Perrigo through (b) (4) (the importer of record) where they are packaged into cartons. The devices are received in Perrigo Allegan where release specification (**EXHIBIT MSM-77**) tests are performed. Tests are conducted on every batch. These activities include review of the Certificate of Analysis from (b) (4) visual review of the pouches, vacuum testing, and chemical testing.

PRE-APPROVAL
(RED)
ANDA # (b) (4) *Cetirizine Dihydrochloride (Cetirizine) 5mg and 10mg tablets*

Perrigo has established a separate Analytical Research and Development entity charged with new product creation and analytical method development. This department performs all development work relating to a new product including critical process parameters, lab method evaluation, impurity profile development and limit establishment. Placebo trials and scale up batches occur during this early phase of the product life cycle with extensive testing and planned manipulations. Biobatch manufacture and further scale up batches are under the control of the Analytical Research and Development team (AR & D). Following successful process development, product and process characterization, and scale up batch execution, the product is transferred to Quality of Commercial manufacturing where and when process validation commences.

The (b) (4) batches of commercial product manufacture are under a period in the product life cycle referred to as "Product Infancy". During this closely monitored period of product manufacture and distribution, all deviations, complaints, out of specification results, and stability data, are scrutinized. A small scale version of the firm's Annual Product Review is performed, named "Product Infancy Report". Should any concerns be raised regarding the product, the product could be either transferred back to the AR &D team for full investigation, or the AR & D team is used as an in house consultant.

To date, Cetirizine has not yet been transferred to the Quality department for commencement of Validation. The product is early on in the review process, and lab methods and technical transfers have also not yet occurred.

The protocol to be followed for this Technical Transfer with Method transfer will include a side by side comparison of a product tested in the AR & D lab with a sample of the same product tested in the Quality Control lab.

The following describes the development work performed to date for Cetirizine 5mg and 10mg tablets:

Cetirizine is manufactured as a direct compression granulation dose proportionally compressed into finished dosage form tablets. The only difference between the 5mg and the 10mg tablets is size/dosage strength.

The manufacture of each finished tablet whether 5mg or 10mg involves two stages of production: formulation of the granulation; compression and coating. Each stage is assigned a separate batch production order number. All equipment and processes used in each stage of manufacture is consistent with equipment and processes already in play at Perrigo. No new equipment or techniques are reported to be required for this product manufacture. Process Flowcharts are provided as **Exhibits # RED 578-579** and **RED 580-581**.

Process Qualification Protocols for both Cetirizine 5mg (Product (b) (4)) and Cetirizine 10mg (Product (b) (4)) were reviewed, copies of which are provided and portions included as **Exhibits RED # 546-562 and RED # 563-577**. The protocol outlines the process qualification procedures and acceptance criteria for scale up production activities, which are then used to support full, commercial scale manufacture.

No new ingredients (beyond the active ingredient) are used in this production, including the coating solution used to coat the tablet post compression.

Blend uniformity studies were conducted without note. Compression samples included analysis of content uniformity and hardness of the finished tablet. Acceptable results were obtained upon completion of each study.

Stability data was also reviewed, with current data to the (b) (4) real time stability mark. All data indicates specifications continue to be attained in all cases. All packaging configurations were also incorporated into the stability study. Stability specifications are provided as **Exhibit # RED 582-583** for 5mg tablets and **Exhibit # RED 584-585** for the 10mg.

Press Qualification studies were reviewed for both the 5mg and 10mg tablets. Challenges included Left and Right Chute low/high weight, hardness, and thickness challenges over high and low press speeds. Challenge samples were pulled over (b) (4) intervals. The reviewed data resultant from these challenges yielded the press specifications in place and fully described in the current batch record for Cetirizine tablet manufacture (5mg and 10mg).

Empower software performs data acquisition, processing, and reporting from chromatography runs through the HPLC system. Data audit trails were verified along with user privileges and security controls without incident. SOP (b) (4) was collected for review and details the guidelines and limitations for users of the software (**Exhibit RED # 586-595**).

Perrigo has received one deficiency letter regarding release testing of Cetirizine with a recommendation for a tighter release specification for dissolution testing. This recommendation has been accepted by Perrigo as verified per Product release specifications (see also Sample (b) (4)). Additionally, during a page by page review of the actual, executed batch record and the record supplied in the submission, 2 pages were noted with minor changes not present in the submission batch record. Specifically, handwritten notations were observed on the actual record at pages 8 and 9 of 19 of the Manufacturing Order while no notations existed in the submission on those same pages. Copies of these differing pages were collected (**Exhibit # RED 596-597**); the firm has committed to sending these updated pages to CDER for inclusion in the submission record (Discussion item # RED 8).

Hold times for the varied stages of Cetirizine manufacture were also reviewed (Summary document supplied as **Exhibit RED # 691**) allowing a (b) (4) hold after each mixing and tablet compression, and 3 months following coating. In addition, a (b) (4) hold time is specified for the coating solution prepared for tablet coating.

These hold times were discussed with management during the inspection (Discussion item # RED 7). Management provided a copy of the cGMP notes dated 12/1995 as source reference for the established hold time limits (which are also extended in other drug product manufacture).

Management interpreted the document to allow for the (b) (4) hold times without supporting stability data to apply at stages of manufacture as they follow at the firm. This matter was further discussed during the inspectional closeout meeting. Dr. Kolodziej responded that hold time studies would commence without delay to support the hold times specified. Additionally, the firm uses the date the first two ingredients are combined as the date of manufacture, with expiration date based on this date.

As detailed above, Perrigo utilizes a (b) (4) approach. Interoffice Memo dated 11/28/06 summarizes the evaluation of Cetirizine into this (b) (4) selected indicator product for each piece of equipment used in Cetirizine manufacture (**Exhibit # RED 598-603**). Additionally, Document Change and Approval Forms with Perrigo Cleaning Validation Memo further detail the assessment of Cetirizine into the established cleaning protocol in place, and requirements to satisfy validation. These documents were copied and are provided as **Exhibits # RED 604-606 and RED 607-609**.

A current, revised commercial batch card for each the 10mg Cetirizine (now referenced as product (b) (4) (versus (b) (4) -development stages) in commercial batch readiness), and the 5mg Cetirizine (now product (b) (4)) were collected for inclusion in this report (**Exhibits # RED 610-637 and RED 638-667**). To these newest batch cards, a minor revision will be made for a typo noticed during inspectional review.

Early developmental work for each dosage strength included scale up batch manufacture using placebo formulations (b) (4) followed by (b) (4) active formulations for the 10mg dosage strength, and (b) (4) active for the 5mg strength. Copies of the summary data obtained and parameter settings for each are provided as **Exhibits # RED 668-669**.

Coating system design and solution development were thoroughly reviewed during this inspection. The process involves the (b) (4) coaters into which pans of compressed tablets are loaded. An automated program ((b) (4)) controls the specific coating parameters per a selected recipe and stops the coating process when the calculated amount of coating solution has been sprayed onto the tablets. In process checks for physical appearance and tablet weight gain are performed by a coating operator and recorded in the batch record.

The computerized coating system development, security and audit trail functions of this program were investigated to ensure the program could perform as designed. The workplace system interface allows only for recipe selection and system start/stop commands. No manipulations to the recipe or parameters are possible without access permission. Additionally, the program provides a printout with each run that is included in the coating batch record. The printout provides evidence of attaining the specified parameters during each run. These printouts are reviewed by Quality as part of the batch record review.

The system allows for a maximum of (b) (4) programs. Though not all are often used, the printout displays each. An example printout from a developmental run is provided as **Exhibit # RED 689-690** and parameter set point example printout as **Exhibit # RED 670-677**.

Tech-Transfer has not yet been completed, though at this point in the development of the product, there are no more planned adjustments, specifications, or parameter modifications. Process Validation will proceed at this point with a planned 3 sequential batch manufactures, which will include the granulation stage followed by compression and coating, though may proceed as either each of the 5mg and 10mg or a combination of both. At the point in the product development that tech-transfer occurs and validation commences, the product is no longer under Analytical Research and Development's control, but rather, now under Quality.

To better understand the data captured within a (b) (4) , a copy of the latest reviewed product was covered: Naproxen Sodium Rx, 250mg and 375mg. The report included sections for: manufacturing orders, modifications, consumer complaints, specifications, and test results. Additionally, data from the commercially distributed lots was compared to the data from the validation batches. No discrepancies or concerns were noted.

MANUFACTURING CODES

Perrigo uses different codes for their manufacturing and packaging operations.

Manufacturing batch code

(b) (4)
(b) (4)
(b) (4)
(b) (4)

Packaging batch code

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

COMPLAINTS/PRODUCT DEFECTS

(MSM)

A review of a summarized list of complaints logged during a two year period extending from 2004 until the current date yielded numerous varying problem categories.

According to Mr. John Nadelin, QA manager Consumer Affairs, as of May 02, 2005, all complaints are outsourced to (b) (4) is a medical based complaint handling business. Operators are medically trained personnel. Changes to the handling procedure were implemented in May 2006 with the addition of (b) (4) (**EXHIBIT MSM226-229**) describes and defines the fields available and the flow of the (b) (4) database. Calls come into (b) (4) or Perrigo through telephone, fax, or email. (b) (4) is still the first line receiver of complaints but now, their duties are limited to answering the calls and conducting some consumer follow up calls for additional information. Complaints are opened and an initial review is performed. The case is processed and a determination is made as to whether or not an investigation should be conducted. Perrigo utilizes three different color files for the hardcopy complaints.

(b) (4) is an Adverse Events
(b) (4) is a quality complaint
(b) (4) is an elevated complaint

Reasons for complaint spikes are discussed in quality counsel meetings which are held monthly. Reviews of complaints are conducted but there is no complete 100% review of all complaints to assure those that should be escalated are in fact done. Management double checks batch records for problematic complaints and deviations.

According to (b) (6) , a member of the Internal Audit team, audits of complaint reviews are conducted. The planed activities include:

1. Review of SOP's
2. Evaluation of the process against the SOP's
3. Evaluation of the process against the Regulation requirements
4. Sampling of records to audit
5. Comparison of audit results to those of the operators

According to John Nadelin, the firm has also changed their procedure in terms of trending complaints. All complaints that meet certain requirements are investigated, regardless of quantity. An investigative action is conducted within (b) (4) days including review of batch records, retain samples, and complaint history. Complaints history is looked at not only by batch number but by product line. In addition, an email alert notification is sent to all management when a complaint receives escalation status. An example of a complaint receiving escalation would be one which alleges two different Perrigo tablets. When a sample is escalated an e-notification is sent to the required individuals (**EXHIBIT MSM 203**) according to SOP (b) (4) (**EXHIBIT MSM 200-202**).

Trending reports have been changed to include more information. (b) (4) reports (**EXHIBIT MSM 136-143**) and (b) (4) reports (**EXHIBIT MSM 144-149**) are now performed.

From the complaint listings provided complaints for suspension products including children's IB (b) (4), Nasal Spray lines, and pregnancy test kits were selected for further review. Within the

production area, products which yielded the top concern were Children's Ibuprofen Suspension regarding the product "being thick and lumpy". Included in the review was DQRS Complaint (b) (4) for Children's Ibuprofen Oral Suspension Grape Flavored Liquid (Product code (b) (4)), lot (b) (4) under the Major Pharmaceuticals Inc. label (Perrigo Complaint # (b) (4)). Both the consumer's returned and Perrigo's reserve samples were analyzed and found to be within specifications.

Extensive review of the firm's Children's IB Suspension ((b) (4) product line was conducted. The firm's APR's for 2004 and 2005 were reviewed including stability data. Perrigo has also started a shipping study to review the conditions of temperature on shipping to determine the stress that weather may have on the suspension products. Studies are done on a worse case scenario.

Roger Reimink, Director of Distribution supplied information regarding the distribution aspect of the study. He informed me that the data was collected for the summer of 2006 and the winter information was in the process of being collected. Temperature studies will also include temperature mapping of the warehouse including the use of portable air units. Products included in the study include suspensions, gummy bears, and the lozenge gums. Mr. Reimink stated that shipping is done using Perrigo trucks between Perrigo plants and contract carriers are used to ship to customers. In a limited amount of cases some customers pick out product, but this is manly from the SC distribution center.

Brain Hoffman, Transportation Manager, provided information relating to the actual study. Mr. Hoffman stated that the purpose of the study is to look at shipping to determine the affect of temperature on products during distribution. During July –August, 30 different shipments over the US were monitored. 1 probe was placed in each shipment. The winter study will include Jan-Feb. the probe will be placed in the coldest part of the shipments. All information will be shared with distribution centers to prevent temperature abuse after it leaves Perrigo's control. The temperature probes are used the check the condition of the truck and not placed in actually bottles of product. The probes will then be sent to (b) (4) who has been contracted out to perform interpretation of the information on the probes. (b) (4) will also perform lab analysis of the product as well.

No special packaging is used by Perrigo with the exception of 1 prescription product that is shipped in a cooler with ice packs. This product is a Promethasine suppository (PC (b) (4)). The product is manufactured in (b) (4) and shipped from (b) (4)

Review of the Children's IB suspension (PC (b) (4)) also included the review of the APR for 2004 and 2005. Review of the APR for 2005 found that Perrigo has implemented changes. According to Mike Reske, Manager Quality Engineering, each department is responsible for the information submitted for their corresponding section. Quality Engineering analyzes the information and then submits the conclusion. Quality Engineering has oversight of the review. Analytical test results for Annual product reviews SOP (b) (4) (**EXHIBIT MSM 155-161**) has also been updated. The analysis of the analytical data is now submitted as a CpK value. The CpK splits the distribution in half and

includes the distance between the averages. The higher the value for the CpK the better. Perrigo has different acceptance levels.

(b) (4) of higher is accepted
(b) (4) is monitored for a year and may be further evaluated
Values less then (b) (4) a project plan to be considered.

During the review of the APR for the PC(b) (4) it was determined that the CpK value for Butylparaben was(b) (4). Perrigo chose to round this value to(b) (4) and therefore passed the result without any further investigation or documented justification as to why it was not further evaluated.

Stability for the PC(b) (4) was also reviewed. Marta Williams, QC Stability manager, provided information relating to the stability data and procedures. Ms. Williams stated that(b) (4) is for accelerated studies and normal room temperature studies are performed at(b) (4) Two reasons for placing the product on stability include the annual lot (one batch per packaging configuration per year for liquids) and investigational. Ms. Williams stated that either she or a stability supervisor does the review and provides the summary information for the APR.

According to the stability protocol for the Ibuprofen Suspension PC(b) (4) as part of the Stability Testing Program (**EXHIBIT MSM127-134**), three lots of each size of PC(b) (4) are to be placed on stability for new sizes and formula changes. Review of the stability records including the Summary of Stability Studies and data Available for(b) (4) Child Ibuprofen Suspension (**EXHIBIT MSM 135 and MSM 363**) found this was not done (see FDA-483 Item #12).

Of the complaints pertaining to Perrigo's nasal spray lines, the firm has included safety warnings on the product to address potential burning of the nasal passages with product usage. No additional problems were noted and the number of complaints has been reduced as of the implementation of the labeling change since the previous inspection.

Review of the firm's(b) (4) data showed evidence that it was not being utilized to it full potential. I informed Mr. Nadelin that the narrative section of the complaint should not be cut and pasted into other sections, but rather those sections should include specific instructions. For example, instructions to the lab for sample analysis or to the quality unit for batch record review. This is evident after review of Complaint Case(b) (4) (**EXHIBIT MSM162-183**). There was also no documented evidence on the(b) (4) print out that narrative letters were sent to the consumer nor was there any documentation of sample requests. In one instance I noted that a batch record was not performed but there was no indication as to why that was not done. I also informed Mr. Nadelin that when samples are available from the consumer they should be collected and then decided if analysis is required. By waiting until Perrigo determines that analysis is required, which can sometimes take 2 weeks as evidence by Complaint Case(b) (4) (**EXHIBIT MSM184-196**) Perrigo runs the risk of no longer having the sample available.

There is no documented protocol to determine when complaints are considered repetitive or when retains, or consumer samples are analyzed. In some instances three similar complaints leads to a request for consumer samples, but in other instances, (b) (4) similar complaints does not.

Medical Device Complaints (MSM)

John Nadelin, QA Manager Consumers Affairs, stated that all complaints for the Pregnancy Test Kits are handled by Perrigo. All MDR's are handled by Perrigo and final determinations of questionable complaints are also made by Perrigo. All complaint write ups come to Perrigo for review by the complaint team.

According to Mr. Nadelin, there have been no MDR's or recalls associated with the Pregnancy Test Kits. In any instance where the device has caused a possible injury, a form letter is sent to the customer and the customer is asked to fill out an Adverse Experience Report form.

Complaints were reviewed from 2004 to the current date. The majority of the complaints dealt with incorrect readings with the final determination of misuse by the end consumer. (b) (4) test kit and packaging changes were made in 2005 to make the product more consumer friendly. Changes included mold modification to prevent flooding and a +/- display. Reading complaints were reduced after the changes were implemented.

The firm operates under a change control for changes to the device packaging and carton. The change is usually requested by the customer (example, (b) (4)). The change is then reviewed by Perrigo to assure compliance with the basic requirements. An Art and Print Request form is then submitted when all changes are signed off as being accepted.

Finished product inspection is conducted at the manufacturing facility with a verification test conducted by Perrigo under test Metho (b) (4) (**EXHIBIT MSM77**). Verification testing includes 1 finished product regardless of lot size. Negative verification testing is completed. Confirmation testing is performed yearly and includes testing on three devices, regardless of lot size, for positive and two negative tests. Perrigo releases the product based on their Finished Product Specification for Pregnancy test kits product code (b) (4) (**EXHIBIT MSM78**).

Deviation (b) (4) dated 11/02/2005 (EXHIBIT MSM 80-MSM 106) was initiated in response to a failed verification test conducted by Perrigo. The deviation investigation concluded that the testing protocol used by Perrigo did not match that conducted by (b) (4) (**EXHIBIT MSM107-111**).

Foreign Tablets

In addition to the above, a listing of complaints/deviations (b) (4) with the description foreign tablets was also requested and provided (See **Exhibit Pjd-677/679**). Due to the system utilized to track complaints and deviations, and the use of key words for sorting, both consumer complaints and

processing deviations are combined when attempting to obtain a listing by subject such as Foreign Tablets.

From this listing all files were requested to be pulled and (b) (4) foreign tablet complaints and deviation investigations were selected for review (those clearly identified as non-Perrigo foreign tablet were not reviewed), however several others that turned out to be mixed with product not belonging to Perrigo, but identified simply as "foreign tablet" were reviewed. The listing included (b) (4) complaints of finding foreign tablets not manufactured or packaged by Perrigo and several more involving contract manufacturers where the foreign product did not belong to either the contract manufacturer nor Perrigo ((b) (4) for example); several complaints where the foreign tablet or capsule were both determined to be Perrigo's product however the time span between packaging events was too great to consider the mix up occurred at Perrigo (for example #(b) (4) the strip packaging had occurred 11/2004 and 8/2006 for the (b) (4) lots involved); investigation (b) (4) (DQRS Complaint (b) (4)) complaint filed after finding 2 Ibuprofen tablets (Logo I-2) in bottle of (same drug product different shape) Ibuprofen caplets (Logo I-2). Investigation noted that although the products had both been packaged on the same line, the packaging line had been cleaned several times in between and therefore was inconclusive; one foreign tablet complaint, (b) (4) where both foreign and non foreign tablets (same product different colors) are packaged by Perrigo and are also both manufactured by the same contract manufacturer ((b) (4) In this case neither investigation was able to find an avenue for the mix-up. (b) (4) also involved (b) (4) 81 mg aspirin products one orange one yellow (one Perrigo mfg. and one Time Cap mfg) the investigation of which could not conclude Perrigo was at fault. Complaint/deviation (b) (4) dated 8/10/06 lead to the recall (b) (4) of (b) (4) by contract manufacturer, Banner, as both the foreign and non-foreign products were manufactured by this contract manufacturer. Complaint (b) (4) was initiated when Perrigo's contract packager found mixed product in strip packaged product that is manufactured and strip packed in (b) (4) (Nicotine Gum). See FDA-483 observation #7 for more information regarding one complaint, (b) (4) involving (b) (4) Perrigo products for which the follow-up was deemed inadequate.

(b) (4) deviations listed involved finding foreign tablets (foreign to the lot in progress) during packaging. Deviation (b) (4) 's investigation concluded that the two products found at the packaging step to be mixed, had been compressed at the same time and that operators responsible for hardness checks in both rooms most likely were responsible for the mix-up. The new uniform modifications were in the process of being instituted but had not for the two individuals involved. Review of the investigations and corrective actions appeared adequate. One deviation listed, (b) (4) , was the result of an employee error which was caught immediately. Perrigo has made many improvements in effort of eliminating all foreign tablet issues (see Packaging and Labeling System section for a description of the changes).

ADVERSE EVENT REPORTING
(MSM)

An ADE inspectional review was conducted during this inspection. Inspection included review of development reports, batch records, and analytical data. No deficiencies were noted. This was accomplished in accordance with CP 7353.001 Enforcement of the Post Marketing Adverse Drug Experience Reporting Regulations. The primary focus was to insure the firm had adequate written procedures for the surveillance, receipt, evaluation and submission of post marketing ADE reports to the FDA. Also reviewed was the firm's compliance with ADE regulations and the submission of accurate and complete reports to the FDA in a timely manner. No problems were encountered during the review of the firm's ADE program.

A list (**EXHIBIT MSM1-3**) of the firm's ANDA and NDA products was obtained. Products selected for the complete review were chosen based on the most recent drug approval dates. These products included; Nicotine Polacrilex Gum USP 2mg mint coated (PC(b) (4)) and uncoated(PC(b) (4)), Nicotine Polacrilex Gum USP 4mg mint coated (PC(b) (4) and uncoated (PC(b) (4)), Nicotine Polacrilex Lozenge 2mg (PC(b) (4)) and 4mg (PC(b) (4)).

All reports issued for the above products were submitted to the agency within the required timeframe. This included the(b) (4) alerts. (b) (4) periodic safety reports submitted to the FDA were also reviewed and appeared to have been submitted within the required timeframes and included all the correct information.

John Nadelin, QA Manager Consumers Affairs, provided me with the information relating to the ADE procedures. Adverse Events are handled under SOP(b) (4) (**EXHIBIT MSM 210-221**). The Field Alert Reports(b) (4) (**EXHIBIT MSM222-225**) is used to define the procedure for issuing and submitting a Field Alert Report for distributed ANDA and NDA drug products in accordance with 21 CFR 314.81. A review of the firm's NDA Field Alerts (**EXHIBIT MSM4-5**) was completed.

Review of consumer complaints in FDA's database was conducted prior to the inspection. Complaints were then matched up to Perrigo's complaints. The majority of all complaints were reported to Perrigo with the exception of a limited number of non critical ones. All ADE events were reported and investigated according to procedures.

According to Eric Kolodziej, Perrigo has started the process of consulting with a Medical Opinion board ((b) (4)). This board is used as a:

1- resource to assess medical risk in terms of recalls
2- research for drug articles (literature searches)
3- Risk evaluation for significant changes to labels.

There are currently no specific written guidelines when(b) (4) is used.

RECALL PROCEDURES
(Pjd)

During this inspection follow-up coverage was given to several of the (b) (4) recall actions initiated by Perrigo since the 8/9-9/8/04 GMP inspection. Attached as **Exhibits Pjd-590/593** is a Recall/Withdrawal Summary and as **Exhibits Pjd-658** is a recall summary documenting where each of the recall products were made (Perrigo or by a contract manufacturer). Recalls selected for coverage included: 1) (b) (4) involving Aspirin 81 mg (product (b) (4)) and an incomplete logo problem; 2) (b) (4) involving Aspirin 81 mg (product # (b) (4)) 24 month stability failure for product labeled with 36 month expiration date; 3) (b) (4) involving Docusate Sodium and foreign tablet found; 4) (b) (4) involving Liquid Antacid with simethicone and low assay results; 5) (b) (4) involving batches of APAP Caplets contaminated with metal; and 6)Recall # (b) (4) involving 325 mg Aspirin tablets and 200 mg Ibuprofen Tablets manufactured with a common raw material found to have microbial contamination;

1) Recall (b) (4)) involving Aspirin 81 mg, product (b) (4) (Perrigo manufactured), resulted from a shift or drift during logo imprinting causing the last number to not imprint on some of the tablets. As described in NOE (b) (4), this problem was noted during the processing of a lot. At the time this problem was noted three lots were in-process and two had already been released and shipped. The recall was limited to those first two shipped lots ((b) (4)). The correction involved using a smaller print size which would allow for drift without an issue. No additional problems have been experienced since the change.

2) The recall (b) (4)) of Aspirin 81 mg, product (b) (4) (b) (4) manufactured), is discussed under FDA-483 observation #5. The problem was noted while conducting delayed release portion (Drug Release Acid Phase) of the (b) (4) stability analysis of this enteric coated tablet. The expiration dating for this product has been reduced from (b) (4) months as a result of this failure.

3) The recall (b) (4)) of Docusate Sodium, product (b) (4) was initiated after finding a foreign soft gelatin capsule (identified as Vitamin E 400 I.U.), in the bulk container of this stool softener laxative softgel. It was determined, after notifying Perrigo's supplier (b) (4) that both the stool softener and the Vitamin E soft gelatin capsules are manufactured by Perrigo's supplier and that a there had been an issue of foreign tablet found and documented in Banner's batch record. Perrigo's recall (initiated by (b) (4)) involved two packaged lots ((b) (4) released prior to finding the foreign capsule during a subsequent packaging run for the same bulk lot.

4) The low simethicone assay was noted during the 3 month stability check for the 12 oz annual stability lot for 2006. It was determined through investigation that this problem was due to inadequate purging of the first portion of the batch during the start of the filling process. Reportedly the tubing associated with the fill process is known to absorb the simethicone and a set quantity of

the batch, which is proportionate to the length of the tubing used, must be purged to waste prior to the start of the fill. The filling equipment is multi-use and PLC driven. Following a recent validation of the Antacid products (April 2006), shorter tubing and thus smaller purge quantities had been assigned this product family. However, failure to update the operator set up directions for the Mint Flavor Liquid Antacid resulted in the use of the longer recirculation line tubing when the PLC portion of the process was programmed for the shorter tubing set up and thus a smaller purge quantity.

Another change was initiated after noting temperature could have an effect on how much simethicone is absorbed by the transfer lines. It was observed that the length of time elapsed between the hot water rinse (cleaning) and the start of the filling operation, had an effect on the absorption. A cold water rinse following the hot water rinse of the equipment was instituted in June 2006. However, stability batch (b) (4) was manufactured before this change was implemented.

During the investigation it was noted that the batches exhibiting low simethicone assay were limited to those with a short time elapse between the hot water rinse the beginning of the fill. In addition, the low simethicone assays were limited to the beginning of the fill bottles. For lot (b) (4) the beginning, middle and end simethicone assays at release were (b) (4) (Limits (b) (4)). The 3 month stability assay result was (b) (4) It is Perrigo's practice to pull stability samples throughout the run. It is believed, however, that for lot (b) (4) the beginning stability samples were pulled prior to the beginning of the run samples that were analyzed prior to release of this lot.

As documented in Unusual Event (b) (4) dated 9/7/06 (**Exhibits Pjd-613/657**) a look back at all lots released with beginning simethicone assays of (b) (4) or less was conducted and the lots were placed on hold. This was later adjusted to assays of (b) (4) or less based on literature documenting the stability of simethicone. Further evaluation was conducted to determine whether a significant amount of time had passed between completion of the wash and the hook up to the packaging line. If time enough to allow the transfer lines to cool had passed the lot was recommended to be released from recall consideration. In addition to the stability lot ((b) (4) which had a (b) (4) minute lapse between rinse and hook up, one other bulk lot (b) (4) was determined to be of concern based on the short amount of time (b) (4)) between the hot water rinse and hook up to the packaging line. The (b) (4) bulk batches had been packaged under a total of (b) (4) different lot numbers. These (b) (4) lots were subject of this recall.

5) For further details regarding Recall (b) (4) Product (b) (4) all lots produced, see metal contamination section above. **Exhibit # RED 16** is a comprehensive list displaying use of all (b) (4) supplied raw materia (b) (4)
A copy of batch record (b) (4) was also collected with related metal detection orders where findings of wire-like fragments in the finished product tablets were first detected (**Exhibit # RED 112-246**).
A Complete list of use of Raw Material (b) (4) is also provided as **Exhibit # RED 678-688.**

6) Recalls (b) (4) involving325 mg Aspirin tablets and 200 mg Ibuprofen Tablets both manufactured with a common raw material – Starch. During a routine recertification of the starch supplier, through the testing of the raw material, it was discovered that there were "hot spots" of microbial contamination. As a result of the raw material investigation two aspirin and one ibuprofen lot were recalled. See also FDA-483 observation 2.A.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

OBSERVATION 1

Written records of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up.

Investigations resulting in For Cause metal detection manufacturing orders lacked documented conclusion and follow up. No comparison of the description and type of metal fragments found and isolated by quality control from rejected tablets, to the deviation initiating the For Cause metal detection run was documented.

For example,

a- metal detection manufacturing orders performed 12/2004 on Acetaminophen 500 mg caplet, product (b) (4) lot numbers (b) (4) resulted in QC lab findings of wire like metal fragments though the deviation was initiated because of plenum wear noted in the coating equipment.

b- metal detection manufacturing order for (b) (4) lot (b) (4) was performed 7/2006 as a result of a deviation investigation (deviation (b) (4)) regarding finding a (b) (4) during compression. The metal detection order resulted in (b) (4) tablets rejected for metal. Fragments isolated by QC from these rejected tablets revealed wire like metal.

In each of the above examples, no further investigation into the wire like metal found by QC from the analysis as part of the initial investigation was performed and documented.

Reference: 21 CFR 211.192

Supporting Evidence and Relevance:

RED

a- On 12/13/04, Deviation Investigation (Perrigo Quality Notification) #(b) (4) was initiated for (b) (4) batch (b) (4) due to plenum and coating pan wear noted on pan 044 (**Exhibit #RED 414**). The investigation expanded the affected batches to include all processed in the damaged coating pan since the time of the last major clean (last documented point in time when no damage was noted). This included batches (b) (4) (both (b) (4) products), and (b) (4) (both (b) (4) products).

100% metal detection of each of the affected batches was performed immediately (12/13-16/04) and resulted in the following:

Product	Lot	# Rejected tablets
(b) (4)	(b) (4)	
	(b) (4)	
(b) (4)	(b) (4)	
	(b) (4)	
	(b) (4)	

It was further explained by Technical operations that the QC lab did not have specifications for the metal content in rejected tablets unless provided as part of the sample request. Thus the # and type of metal fragments found during the special testing did not exceed any specification, as there had not been one.

In this deviation investigation, no further review of the metal fragments found in the tablets rejected for metal was described and the fragments found were not related back to the original deviation (wear and scrapes on coating equipment to wire like fragments found in rejected tablets).

b - Deviation investigation #(b) (4) (**Exhibit #RED 483-489**) initiated 5/28/06 displays a similar pattern of investigation in that the deviation was initiated because a hex nut had been found by an operator during compression operations of (b) (4) (b) (4) , and resulted in a metal detection order yielding (b) (4) tablets rejected for metal (though a (b) (4) was what had initiated the metal detection order). Laboratory analysis of the rejected tablets revealed wire like metal fragments of varying dimensions had been isolated. **Exhibits # RED 473 through 476** are photos of the

isolated metal fragments from tablets rejected for metal in lot (b) (4) One of these fragments in particular measures greater than 10mm in coiled form (**Exhibit #RED 475**).
This deviation investigation was signed off as completed on 7/20/06, (b) (4) before the metal detection run had initiated.

Relevance:
In each of the above examples, evidence that wire like material was found in (b) (4) tablets before lot (b) (4) was ever manufactured (lot with deviation investigation that ultimately resulted in the recall of all (b) (4) tablets (500mg Acetaminophen caplets)).

Particularly, in the 12/2004 investigation listed above, wire fragments were found and isolated by the QC laboratory in (b) (4) caplets that had been rejected for metal. There was no description of where these fragments were located in the tablets (i.e. on the surface, or embedded), or relation of the wire fragments to the deviation.

In the 12/2004 investigation, sequestered batches of product processed in a coating pan that was observed with equipment wear were reworked for metal through a metal detector. The extent of the batches on hold for metal detection spanned to the last time the equipment was documented in good state of repair: at the last Major clean. The metal detection orders resulted in (b) (4) rejected tablets over all 6 lots detected. These tablets were ground up in the lab to reveal certain contained wire like fragments listed above and photographed (**Exhibit # RED 470-471**).

In the 5/2006 investigation, a hex nut was found by an operator. The affected batch was metal detected for cause and resulted in (b) (4) rejected tablets. These tablets were also ground up by the QC lab to reveal a number of wire like fragments. No mention of this finding as part of the deviation investigation is observed.

A review of all metal detection log records was performed. The review concluded that only (b) (4) lots of (b) (4) had ever been processed through the metal detectors, each a for cause event (prior to lot (b) (4) The first (b) (4) of which were (b) (4) (each associated with the plenum wear deviation # (b) (4) – **Exhibit # RED 409-411**). The (b) (4) was for batch (b) (4) as a result of the hex nut investigation (deviation # (b) (4)), and the last, for batch (b) (4) (**Exhibit # RED 410**).

A retrospective review of these metal detection orders and resultant QC isolated fragments was performed during the FDA inspection initiated 11-2006. In this review, Technical Operations was able to physically review the isolated metal fragments and photograph each remaining fragment. A compilation of these photographs taken was provided to the FDA team during the inspection (**Exhibit # RED 470-475**). According to (b) (6) , Associate Director, Technical Support, these fragments were a part of the deviation and were stored with the batch record of the affected batch initiating the deviation.

A review of the procedure in place for Deviation Investigations at the time of the deviation (b) (4) revealed directives were provided to QA to ensure that all information uncovered as part of the investigation be reviewed with the investigation. Specifically, under section (b) (4) (**Exhibit # RED 864**), "(b) (4) ".

Discussion with Management:

Eric Kolodziej stated that this observation had to do with thoroughness of the investigation. Management performed a retrospective review of all previously metal detected lots of (b) (4) including review of the actual metal fragments isolated from the metal detection process (if any) as part of the initial deviation investigation into metal fragments found in (b) (4) Acetaminophen. According to (b) (6) , as part of routine metal detection orders for cause, rejected tablets confirmed for metal are sent to the QC lab for further analysis. Any extracted fragments particles or pieces remaining after this analysis are to be placed in a bag, sealed, and attached to the batch record for the affected lot. These bags are what were reviewed during the retrospective look at previous lots. From this, wire-like metal fragments were observed to have been isolated from those previous lots.

Management agreed that the prior investigations should have included a more complete review of all data found from those earlier analyses. This is summarized as part of the full investigation report into the metal fragments found in lot (b) (4) where it is stated, "(b) (4) ", (**Exhibit # RED 13**).

As corrective action to FDA Observation # 1, the firm has now implemented a requirement to review all metal detection results and QC findings prior to closing the investigation requiring the metal detection. In the future, all samples of rejected tablets obtained through for cause metal detection orders will require full analysis of lab results and fragments before closing out the related deviation.

OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

A. Investigational findings revealing microbiological contamination in a receipt of starch material

((b) (4)), Perrigo Batch Number (b) (4) supplied to the firm for use in products (b) (4) tablet manufacture, resulted in corrective actions including an increase in sampling of this starch material upon receipt of subsequent batches, and review of supplier practices including shipment and storage.

This investigation (Notification #(b) (4)) dated 8/11/05 did not extend to other raw materials to determine if the implemented corrective action should also be applied, or document the rationale supporting the decision not to extend the corrective action.

B. For complaint "Case #" (b) (4) received 10/2/2006, the third complaint received for product (b) (4) related to degradation issues, the investigation is deficient for the following:

1. the Complaint History Evaluation contains the statement that "(b) (4) ".
2. (b) (4) (9/22/06) were also received for this same lot.
3. Examination of the returned consumer sample also noted fibers on the product in the bottle;
4. Lab evaluation and stability data evaluation were deemed to be not in the scope of the investigation without documentation of the rational
5. No stability data to support the 36 month expiration assigned this package size;
6. no root cause was determined and no corrective action required. The lot was stated to be "(b) (4) " based on the results of the investigation.

In addition it was determined that none of the complaints received for this lot were forwarded to the contract manufacturer.

C. For complaint #P(b) (4) 5, received 2/20/06, involving product (b) (4) Exp. date 5/31/07 reported "(b) (4) ", that some of the tablets were stuck together, and that a funny odor was coming from the bottle, the following deficiencies:

1. The documented Product Complaint History noted (b) (4) complaints of bad smell and (b) (4) complaints of tablets sticking together in the previous (b) (4) . Retain samples were not inspected, no testing was performed with out rational. No root cause was determined, and no corrective action was required. This report contains the statement "(b) (4) ." Product stability was not considered as part of this complaint's investigation plan. This product is contract manufactured and there is no indication that the contract manufacturer was notified of the complaint.

Reference: 21 CFR 211.192

Supporting Evidence and Relevance:

2.A.- Deviation Investigation (b) (4) (**Exhibit #RED 692-730**, with attachments) was initiated 8/11/05 due to the finding of microbiological contamination in starch raw material 3170. The findings were the result of sampling occurring as part of a supplier Certificate of Analysis verification program. Inadvertently, a sample from the starch raw material (b) (4) was collected and submitted to the microbiological laboratory for Aerobic Plate Count (APC) analysis as part of a supplier recertification. According to the Supplier Recertification program, only test data provided by the supplier are to be challenged, and for starch (b) (4), microbiological APC is not one of these test requirements under the program (because the supplier does not provide this data on their Certificate of Analysis, but rather Perrigo performs this test as part of the receipt process). Nonetheless, the APC test was performed and results indicated contamination including *Enterobacter sakazakii*. The investigation was initiated, and affected material placed on Hold.

2.B.

Review of the complaints received for Product (b) (4) from 8/1/04 to the present (**Exhibits Pjd-313/323**) noted (b) (4) complaints for lot (b) (4), packaged in 500 count bottles and labeled with 36 month expiration date, related to product degradation (**Exhibits Pjd-318, 321, 322**). The first such complaint, (b) (4) received 1/27/06, reported the product smells like vinegar (see **Exhibits Pjd-277/289**). The packaging lot number (b) (4) indicates the lot was packaged in November (L) 2004. This is a (b) (4), assigned an expiration date of 3/07 based on the contract manufacturer's (Time Cap Laboratory) date of manufacture three years prior. The consumer's returned sample was analyzed and was found to be within specification.

The second such complaint, Case (b) (4) received 9/22/06, reported the product had a vinegar smell and funny sour taste (see **Exhibits Pjd-290/299**). The documented batch review associated with this complaint "(b) (4)" (**Exhibit Pjd-291**) is presumed to be referring to the packaging record review as this product is not manufactured by Perrigo but is packaged by Perrigo. According to 10/6/06 document summarizing this complaint, product stability data evaluation is not in the scope of the investigation nor is a reserve sample evaluation (**Exhibit Pjd-291**). The "Product Info" section for this complaint indicates Perrigo, Michigan is the manufacturing site and the Manufacturing Lot number is (b) (4)9 (**Exhibit Pjd-292**) – this product is manufactured by (b) (4). The lot # (b) (4) would represent the incoming lot number assigned when received in June of 2004. The Batch record review information document (**Exhibit Pjd-297**) for complaint numbers (b) (4) (see below) contains the statement "(b) (4)." Reportedly copies of the

manufacturing batch records from (b) (4) are not provided to Perrigo. There is no documentation that (b) (4) was notified of this or any complaints for this lot. Since all questions and info related to the packaging of this lot were marked "N/A" it is unclear what or where these statements originated about or from. No root cause was determined and no corrective action was required for this issue.

The third such complaint, Case # (b) (4) received 10/02/06, reported the product had "(b) (4) ." This complaint was classified as problem code "foreign matter". The Complaint History Evaluation states "(b) (4) " without mention of the two complaints noted above. The following statement was recorded in the complaint activity log on 10/02/06 "(b) (4) ." (**Exhibit Pjd-305**) The consumer's sample, about ½ of the bottle, was returned on 10/10/06 and evaluated. Fibers were noted to be present on the tablets, however analysis was not performed. On 10/23/06 one previously opened reserve sample was evaluated for the presence of crystals. None were noted. Again no root cause was determined, Product stability data evaluation is not in the scope of the investigation (**Exhibit Pjd-301**); and Corrective action is not required (**Exhibit Pjd-302**).

Two of the above complaints, (b) (4) (received 9/22/06) and (b) (4) (received 10/02/06), were received after the investigation and decision to relabel all (b) (4) product with 24 month expiration dates due to lack of stability data to support a 36 month expiration previously assigned this product in 500 count bottles (see FDA-483 observation #5 below and **Exhibit Pjd-218** which is an example of one of the batches relabeled). No mention of this lack of stability data or the correction initiated for in-house and future batches were associated with these two complaints received for lot (b) (4)

2.C.

Product (b) (4) 81 mg Enteric Coated Aspirin, Complain (b) (4) dated 2/20/06 involving lot (b) (4) attached as **Exhibits Pjd-266/276**. According to the document entitled "COMPLAINT INVESTIGATION PLAN" the extent of this investigation included a "batch record review" and a batch and product history review **Exhibit Pjd-267**. The manufacturing lot number assigned was 4H1719 (**Exhibit Pjd-274**) which indicates the 8th (b) (4) month of 2004 was when the product was received and the packaging lot number (b) (4) indicates it was packaged in December (b) (4) 2004. This is a (b) (4) formula lot, assigned an expiration date of 5/31/07 based on the contract manufacturer's ((b) (4) Laboratory) date of manufacture three years prior. Also since this drug is received in bulk, the documented review of the batch record is limited to Perrigo's packaging record. Since the manufacture was not notified (as there is not documentation that this was done), there was no review of the actual manufacturing record to determine whether or not any manufacturing deviations existed for this lot of product. The "(b) (4) " has a box

entitled "Product Stability Data" which was not checked (**Exhibit Pjd-267**) and there was no documented reason as to why stability is not considered when the reason for the complaint indicates an apparent degradation of the product. As described in inspectional observation #5 of this report, Perrigo had no stability data to support the labeled three year expiration for this product packaged in 500 count bottles. At the time of this complaint, the initial 500 count bottle lot that had been placed on stability in 2004, had only 18 month data. This complaint lot was approximately 21 months old when this problem was noted. A check of the reserve sample for this lot was also not considered as part of this investigation as documented in the "Investigation Summary Report" attached as **Exhibit Pjd-269**, with no justification as to why not.

Complaint Case (b) (4) received 10/6/06 for Product (b) (4) was also reviewed (**Exhibits Pjd-324/335**). This complaint was still open but represents another example of a (b) (4) lot, packaged in 500 count bottle, experiencing degradation issues. This complainant noted most of the tablets had white crystals. As part of Perrigo's follow up, one reserve sample bottle was opened and the individual reported "There was an offensive vinegar odor upon breaking the TEP" and "did not disturb clumped product to inspect logos" (**Exhibits Pjd-331**). Deviation (b) (4) was initiated 10/25/06 as the reserve sample revealed "(b) (4) ." (see **Exhibits Pjd-330**, and the photo attached as **Exhibit Pjd-332**). The attached complaint history by batch (**Exhibit Pjd-334**) notes this is the 2nd foreign matter complaint for this lot.

Post inspection review of the (b) (4) complaint listing (**Exhibits Pjd-313/323**) revealed the following additional complaints for this lot which was packaged 8/27/04 and assigned an expiration date of 4/07:

Date	Complaint #	Reason	Exh.
12/29/05	(b) (4)	Smells Bad	Pjd-318
3/01/06	(b) (4)	Smells Bad	Pjd-319
4/17/06	(b) (4)	Foreign Matter	Pjd-319
9/27/06	(b) (4)	Sick as a dog….intentional vomiting/ is vinegar smell normal?	Pjd-321
10/6/06	(b) (4)	White crystals on aspirin tablets	Pjd-322
11/01/06	(b) (4)	Foreign matter	Pjd-322

Complaint Case (b) (4), received 10/25/06 involving Product (b) (4), also reported tablets sticking together inside the bottle (**Exhibits Pjd-336/347**). This complaint was coded as problem codes "Tablets sticking together" and "tablets disintegrating" (**Exhibits Pjd-338**). One reserve sample bottle was opened and reported "slight vinegar odor upon breaking the TEP" (**Exhibit Pjd-345**). Review of the Batch Record Review Information (**Exhibit Pjd-344**) which lists the mfg. lot # of (b) (4) indicates the bulk tablets would have been received November (b) (4) 2004. This document also states the packaging under lot (b) (4) was completed 1/20/05. This lot was assigned an expiration date of 8/07 (**Exhibit Pjd-338**).

Discussion with Management:

2.A-DISCUSSION with MANAGEMENT

Management stated detecting microbial contamination by sampling alone would not provide sufficient assurance of acceptable raw material for use given the findings of this here referenced deviation investigation. In the case of this particular starch raw material #(b) (4) the corrective action also included an in-depth review of the supplier and the supplier's storage and shipping methods. When asked if any other materials received by the firm could be susceptible to similar problems, management stated none were exactly the same, but agreed that a review of other "natural" type raw materials capable of supporting microbial growth should occur. They further performed a review of all microbiological findings for the last 6 months of receipts of Raw material (b) (4)) to show typical patterns of bioburden (**Exhibit # RED 731-736**)
A copy of the Certificate of Analysis for Raw Materia(b) (4) (lot later found with microbial contamination) and receipt specification is provided as **Exhibits # RED 737-740**.

In addition, a review of other starch materials handled by the firm revealed the other 2 such were of a synthetic form deemed not subject to the same forms of microbial contamination (**Exhibit # RED 743**).

Though no specific documentation exists to confirm that the starch supplier was made aware of the *Enterobacter sakazakii* specifically, Mr. Schrode stated that he thought this comment was probably made verbally during conference calls to the supplier and that the starch supplier did know about the microbial contamination found in the lot.

I reiterated my concern that the supplier be notified for certain of this organism so that they may investigate how the contamination occurred.

In response and prior to close out at the firm, Dr. Kolodziej provided a Profile Team Plan directing research into other natural materials handled by the firm and potentially susceptible to microbial contamination (**Exhibit # RED 742**).

2.B and 2.C – Discussion with Management

It was following my questions pertaining to lot(b) (4) and deviation (b) (4) that I was informed by Eric Kolodziej, Vice President Quality and Compliance that he was going to request the Product Safety Committee reconvene regarding the (b) (4) stability issue. Following their meeting Mr. Kolodziej contacted Detroit District's Recall Coordinator, Sandra Williams, to state their position regarding product still in the market place. The stated position was that they believed based on the risk level that all(b) (4)81 mg aspirin drug product labeled with 36 month expiration date would have been removed from the warehouse shelves following the(b) (4)recalls conducted in 2006. Reportedly(b) (4) of this product is sold to

(b) (4) and they were involved with both recalls. The other (b) (4) is sold to (b) (4) under the (b) (4) labels.

Closeout Meeting Discussion with Management

A-Eric Kolodziej stated that this observation sounded like the same type of issue as #1 and again dealt with the thoroughness of the investigation. Louis Yu stated he realized that the samples were very important to show the difference or similarities between the observation and that cites were boiler points from (b) (4).

B/C- Eric Kolodziej stated that he understood. Investigator Domingo stated that the Key words for SAP were important and that the investigation was not completely looked at but rather only batch records were reviewed. Investigator Domingo also stated that the complaints should be forwarded to the contract manufacture. Eric Kolodziej stated that he agreed.

Eric Kolodziej questioned the fact that stability was not looked at. He stated that the overall investigation dealt with stability. Investigator Domingo stated that was not the case for (b) (4). Eric Kolodziej stated stability had to be considered. Investigator Domingo stated there was no documentation that stability was checked in the complaint investigation write up. Eric Kolodziej agreed.

OBSERVATION 3

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

1. (b) (4) " does not specify that all packaging configurations be included in the statistical evaluation of a given product. Review of the Reserve Sample Inspection Forms completed for the Product Code (b) (4) (Adult Low Strength Enteric Coated Aspirin Tablets) finds no evaluation of lots representing those manufactured by your contract manufacturer ((b) (4) packaged in 500 count bottles. Of the (b) (4) selected for the (b) (4) formula, for the review period covering 4/1/2005-3/31/2006; 8/300's, 4/120's and 1/365 count lots were chosen to represent production years 2003-2006. Representing the 2004 and 2005 batches, only 300 count packaged lots were selected. Formula (b) (4) has been packaged in 500 count bottles since prior to 2002. Examples would include but are not limited to lot numbers: (b) (4) .

2. SOP (b) (4) " was not followed with regard to Process Capability Analysis (Cpk) for product (b) (4) (81 mg Enteric Coated Aspirin) manufactured by Perrigo. The Cpk value for the most recent review period (4/1/2005-3/31/2006)

was noted to be below (b) (4). According to SOP (b) (4) a Cpk value of (b) (4) for the aspirin assay should have resulted in a project plan for product evaluation by Technical Operations. As of 11/14/06 this had not been initiated.

3. SOP (b) (4) " requires an evaluation of the occurrence of the deviation as part of a (b) (4) tool. In the following deviation investigations, there were inconsistencies in the criteria analyzed in determining the occurrence or resultant deviation code entered into the deviation tracking database upon conclusion of the deviation investigation. This information is used in calculating the Level of Investigation required in the current deviation and any subsequent deviations that may be generated. For example:

a- Deviations (b) (4) Acetaminophen 500 mg cool caplet, batch (b) (4) pertaining to (b) (4) Acetaminophen 500 mg caplet, batch (b) (4) both involved damage to a security screen used in raw material charging operations, and both occurred in plant (b) (4)) on Equipment/Line: (b) (4) The occurrence determination for (b) (4) reviewed work orders processed in "Mix" areas of production while (b) (4) reviewed work orders processed in both "Mix" and "Compression" areas of production.

b- Deviation (b) (4) both pertained to product (b) (4) and both resulted in a root cause conclusion that the deviation was due to the raw material - supplier (the same supplier in both deviations). Both deviations also concluded finding foreign material in the incoming supplier raw material. Deviation (b) (4) was coded as Solid Contamination - Foreign while Deviation (b) (4) was coded as Solid Contamination - Metal. Deviation (b) (4) did not appear on a requested list of all deviations pertaining to Metal Contamination.

Reference: 21 CFR 211.22(d)

Supporting Evidence and Relevance:

3.1
SOP (b) (4) (**Exhibits Pjd-348/366**)
Section D does not specify that each packaging configuration be included when selecting representative lots for the year's review. Review of the "(b) (4) " (**Exhibit Pjd-411**) and the various raw data Inspection sheets that were completed for Product (b) (4) "ASPIRIN 81 MG ENT TAB" as part of the annual product review conducted 4/16/06 (**Exhibit Pjd-412/424**) revealed none of the (b) (4) samples selected represented product packaged in 500 count bottles. This 500 count presentation for product (b) (4) has been the subject of numerous complaints related to product degradation (see FDA-483 observation 2.B, 2.C, and 5) as well as a recall (b) (4) due to stability failure. Complaints (b) (4) (**Exhibits Pjd-**

277/323) involve lo(b) (4) ; complain(b) (4) involved lo(b) (4) (**Exhibits Pjd-336/347**); and (b) (4) is the first lot, according to the lot listing document attached as **Exhibit Pjd-232**, produced in 2006.

3.2

SOP(b) (4) " (**Exhibits Pjd-390/396**) describes the analysis of annual review data. Section(b) (4) describes the Process capability (Cpk) results from the annual review analysis and what should be done as a result of the score obtained. As described in **Exhibit Pjd-394**, if Cpk less than(b) (4) is obtained a project plan will be required. In my review of the ANNUAL PRODUCT REVIEW prepared for(b) (4) " (**Exhibits Pjd-405/410**) covering both the(b) (4) product manufactured for Perrigo by(b) (4) and the(b) (4) product manufactured by Perrigo, it was noted on page 5 (**Exhibit Pjd-407**), under Analytical Results, that a Cpk value of(b) (4) was obtained for the(b) (4) Aspirin Assay. Two batches were found to be outside(b) (4) firm's specification). The Conclusion section of this report (**Exhibit Pjd-409**) page 7, contains the statement (b) (4) ." This annual review covered the time period 4/1/05-3/31/06. On 11/14/06 I requested information concerning the project plan for this product. According to Mike Reske, Manager of Quality Engineering such a plan had not been initiated. Attached as **Exhibit Pjd-425** is a list of all current projects initiated as a result of a problem. Although there is an entry for regarding "Aspirin Stability Review" a capability study for 81 mg aspirin is not on this list.

3.3

SOP –(b) (4) the Deviation Investigation procedure currently in place requires a "Measure FMEA Tool" calculation as part of the investigation initiation (**Exhibit # RED 798-807**). Specifically,(b) (4) of the deviation observed. Values of(b) (4) are assigned to the Severity and Detection fields, and a value between(b) (4) to the Occurrence field. Then, the product of the three fields is calculated resulting in an(b) (4) . For any individual(b) (4) value greater than or equal to(b) (4) , a Level II investigation is required.

In each of the examples provided in this observation, a level II investigation was performed due to the severity of the deviation. However, the review process was inconsistent.

a-For example, Deviations(b) (4) (**Exhibit # RED 754-770**) and(b) (4) (**Exhibit # RED 771-780**) both involved damage to a security screen used in raw material charging operations, and both occurred in plant(b) (4)) on Equipment/Line(b) (4). The occurrence determination for(b) (4) reviewed work orders processed in "Mix" (listed as(b) (4) – for buildings (b) (4) – **Exhibit # RED 759**) areas of production while(b) (4) (**Exhibit # RED 771-780**) reviewed work orders processed in both "Mix" and "Compression" areas of production (listed as

(b) (4) (b) (4) listed twice here was explained to be a typographical error – should have read "(b) (4)" on second occasion)- **Exhibit # RED 776**).

b- Deviation (b) (4) (**Exhibit # RED 8-105**) and (b) (4) (**Exhibit # RED 483-489**) each pertained to product (b) (4) and each resulted in a root cause conclusion that the deviation was due to the raw material - supplier ((b) (4) China in both deviations). Both deviations also concluded finding foreign material in the incoming supplier raw material. Deviation (b) (4) was coded as *Solid Contamination – Foreign,* while Deviation (b) (4) was coded as *Solid Contamination - Metal*. Because of this codification, deviation (b) (4) did not appear on a requested list of all deviations pertaining to Metal Contamination.

Discussion with Management:

3.1.

In response to this observation and observation 4 below, SOP (b) (4) was revised. A copy of the draft SOP Revision (b) (4) was provided and is attached as **Exhibits Pjd-367/389**. According to Eric Kolodziej, Vice President Quality and Compliance it was never their intention to exclude any package size from their annual review.

Closeout Meeting Discussion

Eric Kolodziej questioned whether or not the over all issue was procedures not followed or procedures not adequate. Investigator Domingo stated that it could be either or both.

3.2

Eric Kolodziej stated that what was shown was the overall project plan for Aspirin but was not specific to the issue. He stated that there was already a general plan in place for Aspirin.

Project was initiated for the (b) (4) during this inspection.

3.3

During the inspection as the differences were noted, Mr. Schrode agreed that different parameters were examined in the course of evaluation of the two sets of investigations observed here but added that employees were trained to evaluate consistently.

Closeout Meeting Discussion.

(b) (6) s stated that this was a hex nut issue so the classification should be metal and not foreign. John Nadelin stated that Perrigo would have to discuss options so that they are classified correctly in the future. Investigator Domingo stressed that all metal should be foreign.
Mr. Kolodziej specified that perhaps the current mode of failure identification and grouping was too granular, and that perhaps a different approach to grouping deviation types would be necessary. (b) (6) and Mr. Bart Schrode further agreed that in the instances above, different elements were searched resulting in a potentially different (b) (4) number. Though each resulted in a full (Level II) investigation, it was understood that the current system was shown to result in different review parameters and different resulting deviation codes in the above referenced investigations.

OBSERVATION 4

Reserve samples from representative sample lots or batches of drug products selected by acceptable statistical procedures are not examined visually at least once a year for evidence of deterioration.

Representative samples selected for the annual visual exam are not opened and examined for signs of deterioration. Examples include:

Product #	Name	# of Batches Selected	# of Samples Opened
(b) (4)	81 mg Aspirin	(b) (4)	(b)
(b) (4)	81 mg Aspirin	(b) (4)	(b) (4)
(b) (4)	Ibuprofen 200 mg	(b) (4)	(b)
(b) (4)	Mint Liq. Antacid	(b) (4)	(b)
(b) (4)	Loperamide HCl	(b) (4)	(b) (4)
(b) (4)	APAP Ext. Rel Cplt.	(b) (4)	(b)
(b) (4)	Naproxen 250 mg, Rx	(b)	(b)
(b) (4)	Naproxen 375 mg Rx	(b)	(b)

* opened during an investigation which lead to a recall for incomplete logo
** (b) (4) lots packaged in blisters were visually observed but not opened

Reference: 21 CFR 211.170(b)

Supporting Evidence and Relevance:
Pjd
During my review of the various annual product reviews prepared, I noted each had a (b) (4) " as an attachment. This document contains a statement regarding the number of reserve samples inspected, batch numbers reviewed, the results of the review, and a

conclusion statement. For the majority of the records reviewed, the results were recorded as "Pass" and the conclusion indicated no problems were noted. On 11/28/06, a visit to the reserve sample storage area was made at which time the reserve sample process was described to me by the Supervisor. It was determined that if a particular bulk or manufactured lot is selected for the annual review, only one of the packaged lots is actually observed. In addition, the current review is limited to a visual check of the packaging (label and carton), notation whether the lot number and expiration date are legible, and whether the TEP or CRC are in place and functioning properly. If the drug product is visible through the immediate container, such as a blister pack, a check that the correct logo and color are present. If, however, the finished package is an opaque bottle no inspection of the contents is conducted for signs of degradation. When I posed the question "why" with regard to not opening the reserve sample I was told 1) this would destroy the sample, and 2) the stability samples are opened and examined for deterioration.

I requested the completed inspection sheets that were generated for each of these annual reserve sample reviews. The form, Attachment 054-00-2, entitled "I(b) (4) [redacted]" attached as **Exhibits Pjd-348/366**).

Review of the reserve sample inspection documentation for the [redacted] tablet products and [redacted] liquid product listed for this observation noted "N/A" recorded for product inspection as follows:

Product #	Exhibits	Product Name
(b) (4)	**Pjd-412**/424	81 mg enteric coated Aspirin (mfg. by (b) (4))
(b) (4)	**Pjd-426/442**	81 mg enteric coated Aspirin (mfg by Perrigo)
(b) (4)	**Pjd-443/494**	Ibuprofen Tablets 200mg
(b) (4)	**Pjd-495/508**	APAP 650 mg Extended Rel. Caplet
(b) (4)	**Pjd-509/522**	Mint Masanti Liquid Antacid Liquid
(b) (4)	**Pjd-523/536**	Loperamide HCl 2 mg caplets
(b) (4)	**Pjd-537/544**	Rx Naproxen 375 mg tablet USP
(b) (4)	**Pjd-545/551**	Rx Naproxen 250 mg tablet USP

In addition to this lack of evaluation of the reserve samples, the number of lots placed on stability is very small. For example, products 604 Ibuprofen Tablets 200mg:

Product	# of batches mfg.	lots placed on stability
(b) (4)	(b) (4) in 2005	(b) (4) pkg as 750 ct and (b) (4) pkg as 20 ct
"	(b) (4) in 2004	(b) (4) pkg as 750 ct and (b) (4) pkg as 20 ct

I asked Eric Kolodziej whether there was statistical support to justify the number of lots placed on stability. He stated there was none. I pointed out that the number of lots placed on stability for a products such as Ibuprofen Tablets was no where near representative. I further pointed out that the small number of stability projects coupled with not opening reserve samples leaves a tremendous gap in their product stability evaluation process.

Discussion with Management:

In response to this observation, a draft revision to SOP (b) (4) was provided to me by Eric Kolodziej and is attached as **Exhibits Pjd-367/389**. The statement "(b) (4) " has been added to the Annual Product Review of Reserve Samples section of this SOP (**Exhibit Pjd-374/375**).

OBSERVATION 5

Results of stability testing are not used in determining expiration dates.

For enteric coated 81 mg aspirin, product code (b) (4) the decision to label 500 count bottles with a 36 month expiration date was not supported by stability data for this package size. The only available stability data supporting 36 months, for lots produced since 2000, was for 120 count bottles. The only lot packaged in 500 count bottles placed on stability in 2004, lot (b) (4) failed drug release at the 24 month test point. There is no stability data available to support the 36 month expiration date assigned to (b) (4) lots with labeled expiration dates from 1/07 - 1/09.

Reference: 21 CFR 211.166(a)

Supporting Evidence and Relevance:

Perrigo contracts with (b) (4) to manufacture Adult 81 mg enteric coated aspirin for them. Perrigo has assigned product number (b) (4) to this drug. Perrigo receives this aspirin product in bulk and then packages it into various size containers ranging from 120 up to 500 count bottles. Reportedly Perrigo has always assigned a three year expiration date to this product, although prior to 2004 only the 120 count bottle packaged with one desiccant was ever placed into their stability program. Perrigo has been purchasing/repackaging (b) (4) product since late 1998 see **Exhibit Pjd-233**. .

Perrigo also manufactures an Adult 81 mg enteric coated aspirin product which has been assigned product number (b) (4). Perrigo has produced this product since 12/05. All lots of (b) (4) 81 mg aspirin have a 24 month expiration date assigned to them.

In May, 2004, Perrigo placed (b) (4), packaged with one desiccant and assigned lot (b) (4), on stability. This lot was assigned an expiration date of 1/2007. At the 24 month test station, which was analyzed 7/20/06, this lot failed the drug release test (**Exhibit Pjd-24/25**). An investigation was initiated under E-Notification # (b) (4) (**Exhibit Pjd-1/217**). The investigation concluded that coating on some tablets in the batch may be damaged, causing the release of the active ingredient to not be properly delayed" (**Exhibit Pjd-12**) although no issues with the coating were noted prior to this 24 month test station (see paragraph A.2.e. of **Exhibit Pjd-17**). Based on the investigation all packaged lots associated with bulk lot (b) (4) were recalled. All lots of this same formula that were still in house were placed on hold 6/23/06 (**Exhibit Pjd-1**) and ultimately were returned to bulk and packaged with a 24 month expiration date. Attached as **Exhibit Pjd-218** is one example of the "Notice of Hold Form" completed for these lots (lot (b) (4) in this case) as a result of the stability failure observed for lo (b) (4). The reason listed on this document was "Incorrect expiration dating". These lots were released from hold in August 2006 as noted in the 8/9/06 memo attached as **Exhibit Pjd-14** and in the E-Notification pages attached as **Exhibits Pjd-3/10**.

This deviation write-up did not address the fact that the only lot in the stability program representing the 500 count package size had failed. There was no written justification for leaving lots assigned with a 36 month expiration date on the market.

A listing of al (b) (4) lots together with their date of manufacture and assigned expiration date was requested and supplied. This listing is attached as **Exhibit Pjd-232**. Any lots on this list that were manufactured post June 2006 were labeled with 24 month expiration dates as a result of this stability failure. All lots manufactured prior to 6/22/06 had been labeled with a 36 month expiration date. Eight of the lots on this list, those with a "Y" in the "Reworked" column, were among those still in house at the time the stability failure was realized. These are the lots that were returned to bulk and labeled with 24 month expiration date prior to release. Excluding the lots repackaged with 24 month expiration dating (those lot numbers with a (b) (4) in the 2nd position of the packaging lot number representing the months July – November of 2006), and those lots listed with expiration dates of 00/00/0000 (which reportedly indicates the lot was not packaged) there are (b) (4) lots that are within expiration date and on the market with a 3 year expiration date.

As can be seen in the attached reports entitled "Summary of Stability Studies and Data Available for (b) (4) 81 mg ent coated aspirin" (**Exhibits Pjd-234/236**) project (b) (4) was the first project featuring the 500 count bottle. The individual project data sheets are attached as **Exhibits Pjd-236/265**. It was study (b) (4) (**Exhibits Pjd-250/251**), conducted on aspirin stored with one desiccant in the bottle, that experienced a failure at 24 months. There was no project initiated for the

500 count package size in 2005. In 2006 one study was initiated with (b)(4) desiccant and one study was initiated with (b)(4) desiccants in the bottle.

Post inspection review of the prior stability studies revealed the following failures not highlighted in the provided summary reports. The failures are as follows:

Study #	Lot#	Container	Time of failure	Test that failed
(b) (4)		Film	6 month 30C/60RH	Aspirin & Salicylic Acid
(b) (4)		Foil	2 month 40C/75RH	" " " "
(b) (4)		Foil	2 month 40C/75RH	" " " "
(b) (4)		30 Ct.	2 month 40C/75RH	Salicylic Acid
(b) (4)		36 Ct.	2 month 40C/75RH	Salicylic Acid
(b) (4)		120 Ct.	36 month	Acid Phase
(b) (4)		120 Ct.	24 month	Acid Phase
(b) (4)		365 Ct.	18 month	Acid Phase
(b) (4)		180 Ct.	24 months	Acid Phase

* Note: Each of these stability reports contains the notation of "Never marketed" and the date "11/16/06" (**Exhibits Pjd-264/265**). These stability reports were generated 11/15/06 at my (Investigator Domingo) request.

It should also be noted that a similar notation was not made for failed study numbers (b) (4) (**Exhibit Pjd-260**) and (b) (4) (**Exhibit Pjd-262**) which according to the Summary report (**Exhibit Pjd-235**) these were the "annual report" for the years 2000 (entered as 3000) and the year 2002. Perrigo only began to bracket their package sizes for stability purposes in June 2006. Prior to June 2006 only the smallest size package was placed on stability unless a special reason, such as a container or closure change, necessitated the additional stability study. I did not determine the results (action taken) following these 2000 and 2002 stability failures, however the reason for failure appears to be for the same reason (Acid Phase release specification (b) (4)) as the failure of lot (b) (4) (**Exhibit Pjd-250**), which lead to this observation.

Discussion with Management:

In discussing the issue regarding the remainder of the (b) (4) lots on the market that bear a 36 month expiration date, Eric Kolodziej, Vice President Quality & Compliance expressed Perrigo opinion that as a result of the recall of lot (b) (4) in August 2006 ((b) (4)) and the March 2006 recall of lots (b) (4) for (b) (4) on the tablets ((b) (4)) Perrigo believes all lots released prior to August 2006 would have been removed from wholesale customer's warehouses already.

Also discussed was the fact that all of the stability studies conducted on 120 count bottles included one desiccant in the bottle. The 500 count bottles also contain only one desiccant.

OBSERVATION 6

Written procedures are not established for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

1. Written procedures do not exist for the maintenance of product transfer hoses used in the liquids manufacturing processes located in Plant (b) (4) Product transfer hoses are not identified so as to track when they are placed into service. Reportedly a length of service has not been established for these multi product hoses which are cleaned with the same detergent as the holding tanks. For example:

Product #	Name	Lot #
(b) (4)	APAP PSE Free Infant Cherry Drops	(b) (4)
(b) (4)	Ibuprofen Suspension	
(b) (4)	Daytime PE Original 6 hour	(b) (4)
(b) (4)	Children's IB Suspension Berry	(b) (4)
	Moist Nasal Spray	(b) (4)

2. Standard Operating Procedure (b) (4), states that procedure A is used: for manufacturing equipment that will not be used to hold suspension formulas. This procedure was used to clean the 100 gal pre Mix tank (b) (4) after and before product (b) (4) (IB suspension) Batch (b) (4) (IB suspension) Batch (b) (4) SOP (b) (4) states that procedure B should be used for Antacid, Ibuprofen/APAP Suspension Formulas.

Reference: 21 CFR 211.67(b)

Supporting Evidence and Relevance:

6.1.(Pjd)
During our tour of the liquid manufacturing operations in Plant (b) (4) it was noted that the transfer hoses utilized for product transfer were not identified, monitored, or tracked. Similar hoses utilized for water only, cleaned with hot water only, are numbered (etched) and have a life expectancy of approximately 6 months. The multi product transfer hoses are cleaned with detergent and are not monitored at all.

Documents describing each of these transfer hoses were collected and are attached as **Exhibit Pjd-584** (water) and **Exhibit Pjd-585** (product).

6.2.(MSM)
SOP (b) (4) (**EXHIBITS MSM242-245**) states that Procedure A should not be used when the equipment is used to hold suspension products. Procedure A was used before and after manufacturing suspensions as shown in the manufacturing of Batch (b) (4) Infant suspension drops (b) (4) and before Batch (b) (4) Infant Suspension grape and Batch (b) (4) infant suspension Drops as shown in the equipment cleaning and use log (**EXHIBIT MSM-246**). I was informed by management that the reason for this is so that the tank is cold before product being placed into it. Procedure A can be used if there is enough time between cleaning and use to allow the tank to cool. I informed management that this was not how the procedure was written and without documentation that employees are trained in this regards, there is no way to assure that this is being done.

Discussion with Management:

6.1.

Liquid area management indicated a camera was purchased to monitor the purified water hoses but had not considered the product hoses. When asked why, no answer was given.

In response to my observation, I was provided a copy of "DRAFT" SOP (b) (4) " (**Exhibit Pjd-586/589**) which as written only references water hoses and assigns responsibility to (b) (4) " but was verbally relayed as the response to my product transfer hose observation.

6.2
Eric Kolodziej questions whether or not his issue was because procedures were not in place or not followed. Investigator Myrick stated that the issue was more that the procedures were not followed.

OBSERVATION 7

Investigations of a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

Consumer complaint (b) (4) dated 4/4/06 reported finding (b) (4) foreign tablets, identified as Perrigo's (b) (4) (APAP 500 mg caplets) mixed inside a bottle of Perrigo's Naproxen Sodium 220 mg Caplets lo (b) (4) . Investigation conducted under deviation (b) (4) initiated 4/5/06, did not determine a definitive root cause for this deviation. However, it also did not include an evaluation of remaining inventory of the complaint lot despite noting a 4 hour packaging overlap on "adjacent" packaging lines for the complaint lot ((b) (4) and a lot ((b) (4)) of the APAP 500mg caplets product noted by a consumer to be mixed with it.

Reference: 21 CFR 211.192

Supporting Evidence and Relevance:
E-Notification (b) (4) , dated 4/5/06, (**Exhibits Pjd-552/582**) documents the investigation initiated as a result of complaint (b) (4) noting (b) (4) (3) Perrigo APAP 500 mg caplets (logo (b) (4)) found in a bottle of Perrigo's Naproxen Sodium 220 mg, lot (b) (4) , product logo (b) (4) . At the time this complaint was received a portion of the complaint lot (b) (4) remained in inventory and it was placed on hold.

The portion of the investigation documented in the (b) (4) section (**Exhibit Pjd-558**) states a lot of Perrigo (b) (4) was being run on the (b) (4) ". APAP Lot (b) (4)) ran between 04:30 and 18:55 on 8/18/05 (**Exhibit Pjd-558**) whereas Naproxen Sodium lot (b) (4)) ran between 23:00 on 8/17/05 and 08:06 on 8/18/05 (**Exhibit Pjd-557**). Although not spelled out as such there was an approximate (b) (4) time overlap when both products were running on packaging lines in close proximity.

The "Miscellaneous" section of this investigation (**Exhibit Pjd-558**) documents "The Retain samples were inspected and no foreign tablets were found in them". Attachment 6 to this investigation documents this retain "samples" inspection. From the 6 bottle retain sample available, only one bottle was opened and evaluated for foreign tablets.

No samples were obtained from the on hold inventory of lot (b) (4) in effort to further evaluate this complaint.

The root cause analysis was documented as "did not determine a (definitive) root cause for this deviation. No improvements were identified. It was concluded unlikely that the contamination occurred at Perrigo and the remaining inventory of lot (b) (4) was released (see **Exhibit Pjd-554**).

Discussion with Management:
Eric Kolodziej stated that this was another one of those thoroughness issues similar to observations 1 and 2.

In discussing this investigation with Eric Kolodziej he agreed with my observation and allowed that they should have pulled a statistical sample of the remaining inventory of the lot for further evaluation.

OBSERVATION 8

Written production and process control procedures are not followed in the execution of production and process control functions.

Written procedures did not coincide with established in process control documents in the following:

a - Coating solution hold study, SAN (b) (4) supporting coating solution hold times specified a flush of "at least 200mL of solution" through the bottom valve prior to sampling for microbiological analysis. SOP (b) (4), also requires a flush prior to starting the coating process, but does not specify an amount. Additionally, batch card coating instructions reviewed for product (b) (4) were observed specifying only a 100g sample (for appearance testing) required to be collected prior to coating.

b - The Process Qualification Report for this same hold study (SAN (b) (4)) did not encompass a worst case scenario as permitted per incoming raw material specifications regarding microbial limits, particularly for Aerobic Plate Count (APC) limits.

Specifically, as stated in the study, "(b) (4)
".

Additionally, SOP (b) (4)
".

c- Review of deviation (b) (4) dated 12/01/05 for batch (b) (4), product (b) (4) Children's Ibuprofen Suspension, found that the operator failed to notify appropriate personnel when the (b) (4) 2 mixer added an additional (b) (4) of corn syrup for sub lot A. In the operating batch card instructions, the employee is to notify appropriate personnel when the addition of any material added is over (b) (4)

d- SOP (b) (4) Equipment cleaning and use logs states that equipment repairs are to be recorded on the equipment cleaning and use logs. This is not always documented as observed during the review of batch records and equipment logs for line (b) (4). Example Batch (b) (4) (b) (4) line (b) (4) dated 11/28/06.

Reference: 21 CFR 211.100(b)

Supporting Evidence and Relevance:

8.a.(RED)

As stated in the above observation, coating solution hold study, SAN (b) (4) (portions collected, **Exhibit # RED 808-812**) supports coating solution hold times given a specified a flush of "at least 200mL of solution" through the bottom valve prior to sampling for microbiological analysis (**Exhibit # RED 810**). SOP (b) (4) Coating of Tablets, also requires a flush prior to starting the coating process, but does not specify an amount (**Exhibit # RED 813-826**). Additionally, batch card coating instructions reviewed for product (b) (4) were observed specifying only a 100g sample (for appearance testing) required being collected prior to coating (**Exhibit # RED 827-828**).

8.b. (RED)

This same hold study (SAN (b) (4) – **Exhibit # RED 808-812**) did not encompass a worst case scenario as permitted per incoming raw material specifications regarding microbial limits, particularly for Aerobic Plate Count (APC) limits. As quoted in the observation, the low initial bioburden in the raw material used in the coating study would support hold times for material with less than or equal to the (b) (4) APC bioburden.

In review of incoming raw material specifications for various coating agents, none provided had microbial acceptance limits of (b) (4) less APC. In fact, most allowed an incoming bioburden of up to (b) (4) APC.

Because of this and the applicable coating procedure, SOP (b) (4) (**Exhibit # RED 829-832**) which states that "(b) (4) ", assurance that bioburden levels would remain at or below specification during a potential 24 hour hold, did not exist.

8.c.(MSM)

Operating Special instructions for the (b) (4) FM Ibuprofen suspension (**EXHIBIT MSM 267-289**) clearly states that unless otherwise stated the maximum variance is (b) (4)

for amounts between (b) (4) . When management was asked what the operator should do if this target was exceed, I was informed that the operator is supposed to inform management. This was not down the case of Batch (b) (4) (**EXHIBIT MSM 267-289**) with the addition of more then (b) (4) variance of High fructose corn syrup under step 25.This error was not caught by neither the operator nor the check operator and management was not aware of the problem until the batch record review was performed.

8.d.(MSM)

SOP (b) (4) **EXHIBIT MSM 124-126**) is used to provide instructions for documenting products, procedures, and maintenance events performed on equipment. This SOP is not followed in all instances of maintenance as evident by Batch record (b) (4) (**EXHIBIT MSM 295-329**). While the batch record does record the fact that the line was down on the Fill Level Documentation Throughout Shift sheet (**EXHIBIT MSM-315**) it does not specify why the line was down and no maintenance was recorded on the equipment cleaning and use log (**EXHIBIT MSM-291**) for the corresponding period of time that the line was down specifically 11/29/06 from 0230 to 0700. The in process inspection sheet (**EXHIBIT MSM-305**) shows a time difference of 0216 to 1035 on 11/29/06.

Discussion with Management:

8a

Management continually stated that the overfill allowance would assure a complete flush of greater than 200mL, however I specified that the line fill amount provided by the overfill does not assure that the 200mL has been flushed (as in passed out of the line into waste), and that this would only be met if the overfill amount in the lines was allowed to flush or spray as waste for this 200mL quantity. I further added that because the solution is pumped directly from the mixing tank through a valve on the bottom of the tank, and that the tank fills into a leg of piping before filling the body of the tank, that a potential dead leg may exist that does not permit full mixing of the solution in this piping before the valve. Management did not provide any further discussion on this item, but an employee in the coating department stated that though not specifically quantified, a solution color check sample is taken from the tank valve before hooking up to the coating spray system.

8b

Management had already commenced lowering the incoming tolerances for coating material to better reflect actual values typically obtained. Per the microbiology team lead, (b) (6) , in review of all coating material data obtained for APC over the last year plus, only one lot would have been rejected for an incoming APC count of greater that (b) (4) and agreed a more meaningful specification would be applied.

A list of those materials already decreased to (b) (4) is provided as **Exhibit # RED 833**, however it was noted that Raw Material #(b) (4) used as the selected coating agent for the Pre-Approval product, Cetririzine allows for an incoming tolerance yet at(b) (4) for APC (**Exhibit # RED 834-835**). According to (b) (6) this along with other coating materials will be adjusted without delay.

8c

Management stated that because this was a level 1 investigation, the employee did not warrant re training. I stated that there was not even any documentation to show that the employee was verbally told what had transpired. Without being told what he/she had done wrong, how was Perrigo going to prevent this form happening again and possibly lead to a Level 2 investigation. Management stated they were sure he was told but agreed this was not documented. They will also revisit their requirements for Level 1 investigations.

8d

Management stated they will revisit the equipment cleaning and use log to figure out the best course of action to make these logs better reflect all the operations performed.

OBSERVATION 9

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

The method of charging(b) (4) into a tote during manufacture of Acetaminophen 500 mg caplet, product(b) (4) as observed on 11/07/06, revealed metal on metal contact at the hopper - tote interface through which the charged raw material passes.

Reference: 21 CFR 211.63

Supporting Evidence and Relevance:(RED)

As observed on 11/07/06, while loading APAP DC(b) (4) granulation(b) (4)) into a tote in preparation for compression of product(b) (4) a production employee secured on the second tier of the tote loading room was observed allowing each of(b) (4) drums of the granulation fall onto a security screen hopper for discharge into the tote. As each dropped, a loud clang of metal on metal was audible. Mr. Steve Laninga confirmed that there was no gasket or cushioning between the hopper and the tote opening where-in the hopper was set.

Discussion with Management:

Production Manager Steve Laninga confirmed the hopper-tote interface was metal on metal, and acknowledged the method of loading the drums into the tote as observed on 11/07/06 did create contact of the hopper to the tote lip. The concern of any metal on metal contact points in the process of (b) (4) production was relayed to Mr. Laninga and Dr. Kolodziej as it pertained to the investigation into the metal fragments found in the finished (b) (4) tablets.

Mr. Laninga confirmed the tote and hopper were observed for damage or wear prior to use in each tote loading operation, and that none had been found. However, in corrective action to this observation, a new hopper was designed and implemented consisting of a raised hopper with support legs on the outside of the tote preventing the observed metal on metal contact. Within a week of the observation, a new hopper had been implemented, constructed with exterior legs to prevent any form of metal on metal contact. No further objections were noted.

OBSERVATION 10

Deviations from written production and process control procedures are not justified.

(b) (4) Cleaning procedure as documented in the protocol SAN (b) (4) for validation of the CIP 100 cleaning agent, included hand written changes to the directions for batch (b) (4) dated 11/8-9/06 and Batch (b) (4) dated 11/20/06 without justification for these changes or documented evidence that these changes were included in the on going validation of the clean.

Reference: 21 CFR 211.100(b)

Supporting Evidence and Relevance:

Protocol #SAN (b) (4) was issued for changes to the cleaning procedure of the (b) (4) mixer. Hand written changes were made to this SAN in at least two instances including batch (b) (4) dated 11/20/06 (**EXHIBIT MSM330-331**) and (b) (4) dated 11/08-09/06 (**EXHIBIT MSM334-335**). There is no documentation that these changes were discussed with management, or that these changes will be documented as part of the on going validation protocol.

SAN's are System Authorization Numbers. These may be used as temporary changes to operations. In the above instance the SAN was issued for changes to the operation for validation purposes. Hand

written changes to the SAN included the distinction of using hot water and the quantity of water needed.

Discussion with Management:
Eric Kolodziej questioned what the issue was with this observation. Investigator Myrick stated that it was a documentation issue. Investigator Myrick was also informed that hand written changes are not allowed on documents and that these changes should have been brought to the attention of appropriate personnel. Management promised employee training.

OBSERVATION 11

Employees are not given training in the particular operations they perform as part of their function.

Deviation (b) (4) concluded the cause was an error by the operator in dispensing, by failing to tare container (b) (4) prior to dispensing sodium benzoate for sub lot (b) (4) This dispensing failure lead to OOS result for Sodium benzoate in Product (b) (4) (Ibuprofen Suspension). While manpower was found to be the root cause, there is no documentation that the persons responsible were trained in the correct procedures.

In addition, deviation (b) (4) (b) (4) Infant suspension drops Batch (b) (4), noted manpower again as the reason for the deviation. The (b) (4) technician failed to make the required changes to the limit levels for Acetaminophen Assay. While the first line persons responsible were addressed, there is no documentation that the persons responsible for the secondary review, whom also did not detect the reason for the deviation, were alerted of their oversight.

Also, deviation (b) (4) dated 12/01/05 for batch (b) (4) product (b) (4), Children's Ibuprofen Suspension, which resulted in the over addition of corn syrup by (b) (4) did not address the fact that the operator failed to follow the batch record instructions which states that an addition over (b) (4) of any raw material should be brought to the supervisors attention. The deviation did not document any training of the persons involved.

Reference: 21 CFR 211.25(a)

Supporting Evidence and Relevance:(MSM)

Deviation (b) (4) Dated 05/25/2006 (**EXHIBIT MSM345-353**), (b) (4) dated 06/08/2006 (**EXHIBIT MSM336-344**) and (b) (4) dated 12/02/2005 (**EXHIBIT MSM354-**

362) all show evidence that there is no documentation of employees being retrained for operator errors. In Deviation (b) (4) and (b) (4) there is no documented evidence that the errors were even brought to the operator's attention. Deviation (b) (4) shows evidence of the operator being made aware of the error, but no documented evidence of the reviewing supervisor being made aware of his/her oversight during the review process.

Discussion with Management:
Greg Kurdys asked if this was a documentation of no training. Eric Kolodziej stated that these were all level 1 investigations. Investigator Myrick stressed that if Level 1 investigations do not include documentation of training of personnel or even verbal communication to the employee to alert them of the issue how is the firm going to prevent a more serious Level 2 from possibly happening in the future. All level 1's should at least include documentation that the issue was brought to the attention of at least those directly involved. Management stated they were sure the issue was brought to the operators attention but do not have documented proof of that happening.

OBSERVATION 12

The written stability testing program is not followed.

Specifically, Ibuprofen Suspension Product code (b) (4) Stability Testing Program states that the first (b) (4) commercial production lots of Product packaged in each size will be placed on stability. There is no documentation that (b) (4) lots of (b) (4) 8oz were ever placed on stability even though this product has been shipped as evident by lot (b) (4) Also, there is no evidence that the first (b) (4) lots of (b) (4) 4oz or 8oz (which was the result of a formula change) nor the first (b) (4) lots of (b) (4) 4 oz or 8oz (which was also a result of a formula change) were placed on stability as dictated by the stability protocol. All sizes (4oz and 8oz) and formula changes (b) (4) have been released for shipment. The current product code is (b) (4) 4 oz and 8oz.

Reference: 21 CFR 211.166(a)

Supporting Evidence and Relevance:(MSM)

Summary of stability Studies and data for (b) (4) Child Ibuprofen suspension (**EXHIBIT MSM-135 and MSM-362**) shows that the first (b) (4) batch of 4oz were placed on stability as per the stability protocol (**EXHIBIT MSM 127-134**). This protocol was not followed in subsequent stability studies for the initial run of 8oz and upon any formula changes. A change from formula (b) (4) has documented evidence (**EXHIBIT MSM 364**) of a stability waiver, but the formula change from (b) (4)

(b) (4) and the change form (b) (4) does not have the correct amount of samples placed on stability and no documented justification for not following the protocol. (b) (4) samples are also not placed on stability for each size annual as required by the protocol but rather (b) (4) of the 4oz and (b) (4) of the 8oz size is placed on stability.

Discussion with Management:
Eric Kolodziej stated that this was an ANDA submission and that the protocol had been changed for future products.

OBSERVATION 13

Established sampling plans are not followed.

SOP (b) (4) " states that if a batch is stopped prior to completion, then contact must be made to the QC lab, Microbiology lab and Quality to ensure the quantity of samples pulled is appropriate and the reason for being down should be documented on the batch record and Record of Test Samples. There is no documented evidence to assure this step in the procedure is followed when the packaging line goes down. For example Batch (b) (4) AD line 102 dated 11/05/06 and Batch (b) (4) line (b) (4) dated 11/28/06.

Reference: 21 CFR 211.160(a)

Supporting Evidence and Relevance:
Batch (b) (4) (**EXHIBIT MSM 383**) and Batch (b) (4) (**EXHIBIT MSM -315**) show that the line was down for a period of time. No reason is documented as to why the line is line. There is also no indication that the QC lab, Microbiological Lab, and/ or Quality were alerted of the line being down for batch (b) (4) (**EXHIBIT MSM 365-397**) or batch (b) (4) (**EXHIBIT MSM 295-329**) as required by SOP (b) (4) **EXHIBIT MSM 247-266**).

Discussion with Management:
The firm's only response was that they understood.

OBSERVATION 14

The entries in the equipment cleaning and use logs are not in chronological order.

Equipment cleaning and use logs are not in chronological order when the production process is down for any period of time and a line cleaning is perform. For example:
a- line (b) (4) Batch number (b) (4) Daytime PE 6Hr Original Liquid (b) (4)) shows production start of 11/28/06 at 2225 and end production at 11/30/06 at 0045. The next entry was a Cleaning SOP (b) (4) Part 4 performed on 11/29/06 at 1058 and ended at 11/29/06 at 1114. The restart of the production lot was not entered on a separate line after the cleaning entry.
b- line 102 Batch (b) (4) IB 100mg Children Suspension (b) (4)) started production at 11/29/06 at 0200 and ended 11/30/06 at 1450. The next entry was a cleaning procedure SOP (b) (4) Part 2 performed on 11/30/06 at 0810 and ended 11/30/06 at 0936. The restart of the production lot was not entered on a separate line after the cleaning entry.

Reference: 21 CFR 211.182

Supporting Evidence and Relevance:

14.a
Packaging Batch record (b) (4) (**EXHIBIT MSM 295-329**) Fill level Documentation throughout Shift sheet (**EXHIBIT MSM315**) shows stated evidence that the line was down on 11/29/06 from 0230 to 0700. Equipment cleaning and use log (**EXHIBIT MSM 291**) does show a cleaning step (one on 11/29/06 from 1058 to 1114) was performed before the completion of the batch filling operation on 11/30/06 at 0045. The restart of the line, after cleaning, at 1306 on 11/29/06 (see **EXHIBIT MSM 317**) was not documented as a separate entry on this log.
14. b.
This was also evidence by Batch record (b) (4) (**EXHIBIT MSM 399-425**) .The Equipment Cleaning and use log (**EXHIBIT MSM 426**) shows the batch started on 11/29/06 at 0200 and ended on 11/30/06 at 1450. There was a cleaning entry on the same equipment cleaning and use log (**EXHIBIT MSM 426**) on 11/30/06 at 0810. The restart of the line, after this cleaning, at 10:30 on 11/30/06 (**EXHIBIT MSM 417**) was not entered on the log. There is no documented evidence on the Target control sheet (**EXHIBIT MSM 414, MSM416**) the Fill Level Documentation throughout shift sheet (**EXHIBIT MSM 415, MSM 417**) nor the Record of Test samples (**EXHIBIT MSM418**) but there is however written documentation on the Line Clean Up 102 line (**EXHIBIT MSM422**) that shows evidence that the line was idle for 27 hours and 30 minutes.

Discussion with Management:
Eric Kolodziej stated that the firm was looking at options to change the way information is imputed onto the logs.

OBSERVATION 15

Written records of major equipment maintenance are not included in individual equipment logs.

Maintenance on lines is not always written on the equipment cleaning and use logs as noted during the review of batch records and entry logs for line (b) (4) . Example Batch (b) (4) line (b) (4) dated 11/28/06.

Reference: 21 CFR 211.182

Supporting Evidence and Relevance:

SOP (b) (4) " (**EXHIBIT MSM 124-126**) is used to provide instructions for documenting products, procedures, and maintenance events performed on equipment. This SOP is not followed in all instances of maintenance as evident by Batch record for PDT Daytime PE Orig 6 hr Liquid batch (b) (4) (**EXHIBIT MSM 295-329**). While the batch record does record the fact that the line was down on the Fill Level Documentation Throughout Shift sheet (**EXHIBIT MSM 315**) it does not specify why the line was down and no maintenance was recorded on the equipment cleaning and use log (**EXHIBIT MSM 291**) for the corresponding period of time that the line was down specifically 11/29/06 from 0230 to 0700. The in process inspection sheet (**EXHIBIT MSM 305**) shows a time difference of 0216 to 1035 on 11/29/06.

Discussion with Management:
Eric Kolodziej again stated that procedures will be changed to address the way information is entered into the logs.

OBSERVATION 16

Equipment and utensils are not cleaned at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, premix tanks are used to hold cleaning solution (b) (4) for in line cleaning of line (b) (4) as part of SOP (b) (4) Part 1. No verification testing has been documented to show that (b) (4)

Part A is adequate to remove any residue from (b) (4) before being used to pre mix product for the (b) (4) Both the (b) (4) and the premix tanks have not been validated to be cleaned with (b) (4). For example the premix tank ((b) (4)) was used as part of the cleaning of line (b) (4) on 11/27/06 and then a (b) (4) Part A clean was done of the premix tank on 11/27/06 before being used to premix product for Lot (b) (4) (b) (4) on 11/28/06.

Reference: 21 CFR 211.67(a)

Supporting Evidence and Relevance:

Equipment cleaning and use log for (b) (4) (**EXHIBIT MSM 427**) shows that the tank was used for various cleans from 11/10/06 to 11/27/06. Upon further investigation it was determined that the tank is used to hold the cleaning agent used to clean line (b) (4) Line (b) (4) has been under validation to be cleaned using (b) (4) has not been validated to use this cleaning solution. After storing the (b) (4) cleaning solution, this pre mix tank was rinsed with hot water under SOP (b) (4) part A (**EXHIBIT MSM 242-245**). There is no documented validation evidence to show that this hot water rinse is adequate to remove residue of (b) (4), and cleaning verification swab samples were not collected. The firm is currently in the processes of validation the use of (b) (4) in both the (b) (4) and the pre mix tanks but this validation was not complete at the time of these entries.

Discussion with Management:
This issue is currently being addressed with the start of a line (b) (4) premix tank Cleaning study. Line (b) (4) clean was validated under SAN (b) (4) and found to be adequate to remove the (b) (4) cleaning agent. At the close out of the inspection (b) (4) of the premix tank were sampled and there was no residual (b) (4) detected in any of the samples.

OBSERVATION 17

Batch production and control records do not include complete information relating to the production and control of each batch.

Batch records do not always include the reason the line was down as dictated by the SOP (b) (4) For example: (b) (4) date 11/05/06 the line was down between 0706 and 2002 without documented reasoning for this down time.

Reference: 21 CFR 211.188

Supporting Evidence and Relevance:

SOP (b) (4) " (**EXHIBIT MSM 247-266**) clearly states that documentation is to be recorded on the batch record and Record of Sample the reason for stopping packaging. Batch (b) (4) (**EXHIBIT MSM 365-397**) (b) (4) Ibuprofen Suspension which is filled on Line (b) (4) was down on 11/05/06 from 0706 to2002. There is no documented evidence on the batch record as to the reason the line was down.

In addition, as documented in observation 2.B and 2.C. above, complaint investigations routinely include a review of the batch record (**Exhibit Pjd-267, 291, 301, 328, 342**) in an effort to determine whether any problems occurred during the manufacture or packaging of the batch that may have lead to the particular complaints.

Discussion with Management:

Management stated they will address the issue of filling the log sheet out so that there is more of a time line history. They also stated they will address the issue of recording why production stoppages, including filling operations, are not recorded in the batch records.

OBSERVATION 18

Representative samples are not taken of each shipment of each lot of components for testing or examination.

Specifically, sampling of pumps, product code (b) (4), used in nasal products is not representative of the lot. Verification testing for the pumps includes one sample regardless of lot size. Deviation (b) (4) for bent spray nozzle for lot (b) (4) dated 10/5/05 for product (b) (4) batch is an example of this. Incoming inspection of product (b) (4), 8/27/05, (b) (4) out of (b) (4) pumps received was visually examined.

Reference: 21 CFR 211.84(b)

Supporting Evidence and Relevance:

Component/Pre Print Inspection Form for Material (**EXHIBIT MSM441**) [redacted] batch (b) (4) dated 08/27/05 shows documented evidence of the incoming inspection of the caps used for batch (b) (4). Only (b) (4) was inspected. Deviation (b) (4) (**EXHIBIT MSM428-446**) was opened as a result of loose caps found at the labeler. Subsequent rework was performed on Batch (b) (4) Even though the rework found several bent spray nozzles, the subsequent incoming inspection protocol was not increased as a result of the deviation.

Discussion with Management:

Although the subsequent inspection for the caps was a verification sample, I stressed that this was a result of the incoming lot being the [redacted] shipment and the issue of a possible supplier problem was not addressed.

OBSERVATION 19

Complaint records are deficient in that they do not include the known reply to complainant.

Specifically, complaint files do not always include a copy of the reply sent to the complainant and hard copies of the complaint handling program ((b) (4) does not show documentation that the "type of letter" field is always complete when and if a reply is sent. For example closed complaint (b) (4) dated 11/29/06, (b) (4) dated 11/29/06.

Reference: 21 CFR 211.198(b)(1)

Supporting Evidence and Relevance:

Complaint (b) (4) (**EXHIBIT MSM 447-455**) and Complaint (b) (4) (**EXHIBIT MSM 456-463**) do not have hard copy documented evidence that a response was sent to the complainant. Both of these complaints were for the Pregnancy test kits.

Discussion with Management:
Management stated that (b) (4) is not known for their complaint investigations and that Perrigo felt it was best to handle the complaint internally. I stated that while Perrigo should be responsible for answering questions that may impact their product, according to Perrigo, (b) (4) is ultimately for the finished product and therefore should be made aware of all complaints. In further discussion I stressed that this does not mean that Perrigo should stop taking any pregnancy test kits complaints, Perrigo stressed they would not do that. I also stated that this is also true for their other products that are contract manufactured. I stated that the contractors should be aware of complaints received for product that the contract manufacturers make. This is along the same lines that Perrigo should require all of their contracts to inform them of any recalls that could possibly affect Perrigo product or operations.

REFUSALS
No refusals were encountered during this inspection.

GENERAL DISCUSSION WITH MANAGEMENT
Pjd/RED/MSM

A closeout meeting with management occurred on 12/15/06. Perrigo was represented by management staff consisting of Mr. Hendrickson, Dr. Kolodziej, Dr. Yu, (b) (6), (b) (6) and (b) (6) as further detailed on a sign in sheet provided (**Exhibit # Pjd 583**).
The FDA 483, List of Inspectional Observations was presented to Mr. Hendrickson who confirmed he was highest ranking at the firm in the absence of Mr. Papa, CEO.

Verbal Discussion items were also conveyed to the management team during this session as listed below.

Pjd DISCUSSION ITEMS
1. Stability data in Annual Product Review (APR) is not complete. While reviewing APR for product 81 mg Aspirin (product (b) (4)) it was noted that the stability summaries included in this APR did not include any of the current ongoing studies. According to the Stability Manager, Marta Williams, only the completed studies which supported the expiration date are included in the APR's. I pointed out that since the purpose of this document is to review the current state of the product line, including any problems, etc. that it would be more to the point to include all ongoing stability studies for the product line as well as data to support the current assigned expiration date. Dr. Kolodziej stated that he agreed.

2. During this inspection I also discussed with Dr. Kolodziej the fact that their policy of placing only one lot on stability (one lot of the smallest and one lot of the largest sizes effective June 2006) does not provide them with much data to fall back on. For instance with the stability failure experienced for the 81 mg aspirin at 24 months (Recall (b) (4) . They had no other data to fall back on when their one and only lot representing 500 count bottles packaged in 2004 failed. I reminded him that the stability sample(s) are suppose to represent all other lots manufactured that year. Dr. Kolodziej stated they would have to further evaluate this but agreed in principle.

3. Hairnet issue noted during our tour of the liquid filling area in Plant (b) (4) was mentioned. One employee, an operator who was observed loading bottles into the hopper, was noted to have hair outside of her head covering. This was pointed out to management at that time and correction was made immediately.

4. Time stamping samples at the time they are pulled was discussed at length during this inspection. This became an issue during my review of recall (b) (4) initiated for (b) (4) lots of liquid antacid. The fact that the 3 month stability sample was found to have a lower simethicone assay than the beginning of the run samples it was suggested that the stability samples had been acquired prior to the beginning of the batch samples. Had this been the reverse, the lot would not have been released and the recall could not have been necessary.

RED DISCUSSION ITEMS

1- Swab recovery studies did not include all surfaces swabbed/sampled as part of the Plant (b) (4) Tablet Compression machines cleaning validation program.
Exhibit # RED 836-839 display the swab site locations and surfaces as part of the original swab study (**Exhibit # RED 840-841**).
Response:Prior to the inspection closeout, this discussion point had been addressed with a full surface recovery protocol covering the metal surface – anodized aluminum not specifically referenced in the initial swab recovery study. (b) (6) of validation commented that the thought process was that the recovery from different metal surfaces would be the same, but performed the study nonetheless as corrective action. A copy of this protocol is provided as **Exhibit # RED 842-844**, signed and dated 12/05/06.

2- Metal Detection Manufacturing Order Card, Revision (b) (4) completed in the for cause metal detection run performed for part of batch (b) (4) product (b) (4) 8/20-22/06 did not include description of the 20.1Kg of substandard product resultant (**Exhibit # RED 247-260**).

Response:As a result of this discussion item, future metal detection orders will require a detailed description of substandard waste, whether due to spill, equipment waste, or tablets rejected for metal.

3- End of run challenge of the verification metal slugs is not required in sop though in practice, is performed every (b) (4) of metal detection runs (verified corrected).

Response:This verification was amended within a week of notation to include an end of run challenge.

4- The mechanical mortar and pestle used in metal detection order lab analysis was observed to be in need of repair including a chipped bowl and cracked rubber type flange.

Response:As of the close of the inspection, this piece of equipment was reported to have been removed from the lab and placed out of service.

5- Metal Detection order for batch (b) (4) was performed (initiated) (b) (4) after the deviation resulting in the order to metal detect was closed out and signed completed. This is evidenced on the date of initiation of the order as displayed on **Exhibit # RED 502** and **Exhibit # RED** (b) (4) – for deviation sign off for this same lot).

Response: No specific additional comments were provided regarding this discussion point. This point was noted during the last hour prior to the (b) (4) meeting, when a requested document was provided.

6- Regarding the same above (b) (4), there was no documentation in the batch record as to why the line was down on 5-28-06 though the deviation states that a hex nut was found during compression at this time.

Response:See 5.

7- Hold time studies are not conducted as part of process validation to ensure (b) (4) of holding in process materials conform to specifications. In the above deviation, a (b) (4) hold between the time the tablets of batch (b) (4) were compressed until the time they were coated was observed.

Additionally, SOP (b) (4) (**Exhibit # RED 845-850**) provides detailed instructions on hold time limits. This procedure defines a (b) (4) time for granulations from date of manufacture, (b) (4) Hold time for mixes requiring further processing before packaging, and a (b) (4) Hold time allowance for products to be coated (must be coated within the (b) (4) period) in addition to other Hold limits (**Exhibit # RED 847-848**).

Response: Hold time studies will be developed. No further specifics were shared at that time.

8- There was a 2 page difference in review of the pre-approval submission for cetirizine dihydrochloride (Cetirizine) compared with the executed batch records (**Exhibit # RED 596-597**).

Response: These 2 pages would be sent to the agency without delay, for inclusion in the submission.

MSM DISCUSSION ITEMS

1- During the Plant walk through on 11/07/2006, an employee was observed taken tablets that had fallen on the floor and throwing them into the trash barrel instead of the scrap bucket. Management stated that this was not common practice and all employees will be reminded of what material goes into trash and what material should be placed into the scrap bucket.

2- The use of multiple options for description of complaints was discussed with management. (b) (4) has 3 pages of Problem types and Codes (EXHIBIT MSM197-MSM199). Stress was put on the fact that with multiple options, trending is harder to accomplish. Options are not clearly defined and metal can be classified as foreign material or metal. Management stated they will look at options to make the description of complaints more universal.

3- Samples are not always obtained from consumers when available. I stressed to management that when samples are available they should be requested and then the determination to be analyzed can be made after the receipt of the sample. I informed management that in most instances, the consumer or pharmacy will not keep the product for 2-3 weeks until Perrigo makes the determination to analysis the sample and if Perrigo decides at a later to analysis the sample, it may not longer be available. Management stated that they will request all samples in the future unless the product is a bio hazard.

4- (b) (4) is not used to its full potential. Available fields are not being filled out and each separate heading is not being filled out with appropriate information but rather the complainant narrative is being cut a pasted. Management stated that they will address the (b) (4) issues and hope to learn to better use the system as they get more familiar with it.

5- Issues with trending reports included:
   a. The monthly reports did not include severe or problematic complaints. The trending was used for the top five common occurrences, but did not include instances of severe or problematic complaints if they fell outside of the "top five" occurrences.
   b. Number of deviations as a result of complaints was not included in the trending reports.
   c. Information for Adverse Events is limited. The use of the "other" field is not clearly defined and therefore management is not able to assess the severity of the Adverse Event.

Management will address the issue the trending reports to assure they are being reported and used as intended.

6- There is no documentation for regulatory changes for labeling changes made to the Tussin DM product for (b) (4) in 7/24/06-9/6/06 (EXHIBIT MSM204-MSM209), including who made the decision to change from 14mg to 15mg of Phenylalanine. Raw Material supplier change content is not documented as reviewed by regulatory Affairs. Management stated that Perrigo has started implementation of a program (b) (4) that addresses these issues.

7- During Lo (b) (4) a prevalidation was performed in the middle of the batch. During review of the batch records it could not be clearly identified where the prevalidation batch ended and where the released batch restarted. Management stated that prevalidation is no longer performed during the production of released batches.

8- During the walk through of Plant (b) (4) line (b) (4), bottles were observed pulled off the line. When an operator was asked as to why, the response was he was not aware as he was filling in for another employee. Stressed was placed to management that bottles are that are pulled should be clearly identified so that replacement employees will not inadvertently place then back on the production line. Management stated they will look into identifying rejected material more clearly.

9- Record review of Deviation (b) (4) dated 03/24/2005 Batch (b) (4) Children's Ibuprofen suspension (EXHIBIT MSM29-MSM73) showed that samples taken and analyzed to bottle 120 had failing results and were rejected. There is no concrete evidence to show that bottle 121 passed. (b) (4) samples were pulled from the back tier of the storage rack. The back row holds ~23-24 bottles. These bottles are filled in single file and can forma triangle when filing in and therefore the 3 bottle on the back row can be the 10th bottle down the line. Therefore there was no assurance as to what bottle numbers were samples form the back line and whether or not there were failures on the 2nd, 3rd, 4th row. Management stated they will review their sample procedure to assure this is more clearly defined.

10- All complaints should be shared with (b) (4) for the pregnancy test kits as they are ultimately responsible for the finished product. Management stated this will be done.

SAMPLES COLLECTED
(RED)
Sample (b) (4) was collected as a Profile Sample of the Applicant's (Perrigo's) ANDA submission for Cetirizine Dihydrochloride (Cetirizine) 5mg and 10mg tablets, ANDA (b) (4).

Sample DOC(b) (4) is a documentary sample collected showing shipment and receipt of Acetaminophen(b) (4) Direct Compress granulation, lot(b) (4) from(b) (4) China to firm for use in the manufacture of product(b) (4), Acetaminophen Extra Strength Caplets, lot(b) (4). Manufacturing lot#(b) (4) was then packaged into finished product distribution lot #(b) (4) Lot #(b) (4) was manufactured and packaged during August 2006. By 10/10/2006, all but 696 units of the Finished Product lot #(b) (4) had been released and distributed.

The significance of Acetaminophen Extra Strength product(b) (4) lot#(b) (4) is this lot was manufactured with portions of the same raw material,(b) (4) Acetaminophen 90% Direct Compress, lot(b) (4) used in production of Acetaminophen Extra Strength Caplets, lot(b) (4) which resulted in an investigation due to metal contamination and ultimately triggered the recall of all lot of Acetaminophen product(b) (4)

VOLUNTARY CORRECTIONS
(RED)
Corrective actions are also described under the metal contamination section of this report and in the Discussion with Management sections of Observations listed. In addition, Perrigo voluntarily recalled all lots of product(b) (4) ever manufactured as a result of Investigation #(b) (4).

EXHIBITS COLLECTED

Pjd-1/231	Deviation(b) (4) Stability failure for Product(b) (4) Aspirin 81 mg enteric coated tablets, packaged in 500 count bottles, at 24 months and associated documents;
Pjd-232/233	Listing of non-expired(b) (4) lots and Listing of date of first shipments of the various package sizes for(b) (4)
Pjd-234/265	Stability data for Product(b) (4) 81 mg enteric coated aspirin manufactured by (b) (4)
Pjd-266/276	Complaint #(b) (4) pertaining to Product(b) (4) 500's lot(b) (4)
Pjd-277/289	Complaint(b) (4) pertaining to Product(b) (4) 500's lot(b) (4)
Pjd-290/299	Complaint Case #(b) (4) pertaining to Product(b) (4) 500's lot(b) (4)
Pjd-300/312	Complaint Case(b) (4) pertaining to Product(b) (4) 500's lot(b) (4)
Pjd-313/323	Product(b) (4) complaint listing 8/1/04 – 12/6/06
Pjd-324/335	Complaint Case #(b) (4) pertaining to Product(b) (4) 500's lot(b) (4)
Pjd-336/347	Complaint Case(b) (4) pertaining to Product(b) (4) 500's lot(b) (4)
Pjd-348/366	SOP(b) (4) '(b) (4)
Pjd-367/389	SOP(b) (4) (b) (4) (Draft)
Pjd-390/396	SOP(b) (4) '(b) (4)

Pjd-397/404 NOT USED
Pjd-405/410 Annual Product Review Product (b) (4)
Pjd-411/424 Reserve Sample Review for Product (b) (4)
Pjd-425 Listing of current ongoing problem projects
Pjd-426/442 Reserve Sample evaluation documentation Product (b) (4)
Pjd-443/494 Reserve Sample evaluation documentation Product (b) (4)
Pjd-495/508 Reserve Sample evaluation documentation Product (b) (4)
Pjd-509/522 Reserve Sample evaluation documentation Product (b) (4)
Pjd-523/536 Reserve Sample evaluation documentation Product (b) (4)
Pjd-537/544 Reserve Sample evaluation documentation Product (b) (4)
Pjd-545/551 Reserve Sample evaluation documentation Product (b) (4)
Pjd-552/582 Deviation (b) (4)
Pjd-583 Close-out attendance listing (Perrigo)
Pjd-584/585 Water and Product Transfer Hose description sheets
Pjd-586/589 Draft SOP (b) (4) "
Pjd-590/593 "RECALL/WITHDRAWAL SUMMARY" Calendar Year 2005 and 2006
Pjd-594/602 Active Formula List
Pjd-603 Projects Launched FY06
Pjd-604/605 Approved Purchased Products List
Pjd-606/612 Tablet ID List (logos)
Pjd-613/657 Deviation (b) (4)
Pjd-658 Recall/Withdrawal Summary
Pjd-659/676 Prescription Drug Labeling
Pjd-677/679 Foreign Tablet Complaint/Deviation listing

RED 1-4 Company Chain of Command
RED 5-7 Chain of Command – Deviation E-notification list
RED 8-105 Investigation (b) (4)
RED 106-111 Product (b) (4) Batch Revision History
RED 112-246 Batch (b) (4) (Product (b) (4) – Manufacturing Batch Record
RED 247-260 C of A and Metal Detection Order for First Special Sample Testing of (b) (4)
RED 261-277 C of A and Metal Detection Order for second Special Sample Testing of (b) (4)
RED 278-281 (b) (4) Deviation investigation Timeline
RED 282-285 Contract Firm's Medical Risk Assessment – Metal Fragment Contamination

RED 286-287 Lab results of Special Sample Testing– (b) (4) , (b) (4) product Metal Detection
RED 288-291 Photocopy of fragments isolated from lot (b) (4), (b) (4) Metal Detection Sample Testing
RED 292-294 Raw Materia (b) (4) – Rare Earth Magnet Sampling Protocol
RED 295-301 Raw Materia (b) (4) – Special Sample Results from Rare Earth Magnet sampling
RED 302 Photocopy of actual fragments sent to Contract lab for metal analysis (b) (4))
RED 303-337 Contract Lab Final Report re:Findings from Metal analysis from RM (b) (4) and Finished product (b) (4) lo (b) (4)
RED 338-358 Contract Lab Final Report re:Findings from Metal analysis from Finished product (b) (4) lo (b) (4)
RED 359-360 Perrigo summary of Contract Lab findings re: all metal analyses
RED 631-366 Sample protocol – sampling of RM (b) (4) from bulk drums and findings
RED 367 Summary of metal contact equipment used in (b) (4) process.
RED 368-369 Engineering Set Points for Tablex Metal Detection Units during EQ
RED 370 Letter from Tablex Supplier
RED 371-373 EQ summary sections – Metal Detection Units, SAN (b) (4)
RED 374-379 Certificates of Conformity for Calibration Units used in Metal Detection unit Operations
RED 380-382 Installation and Validation time line for all metal detection units
RED 383-408 SOP (b) (4)
RED 409-411 Metal Detection Logs (for product (b) (4) over prior two year period)
RED 412-413 Metal Related Metal Deviations List
RED 414-476 Deviation Investigation (b) (4)
RED 477-482 Procedure (b) (4) Foreign Matter in Raw Material, Tablet Mixes, or Granulation
RED 483-489 Deviation Investigation (b) (4)
RED 490-512 Portions of Batch (b) (4) with Metal Detection Order
RED 513-515 SOP (b) (4)
RED 516-517 SOP (b) (4))
RED 518-519 Photographs of particles/fragments isolated from (b) (4) tote charging
RED 520-521 Sieve Equipment/Screen Questionnaire
RED 522-528 (b) (4) FM APAP 500mg Caplet Annual Product Review (most recent)-Portions of
RED 529-544 Cleaning Validation Master Plan
RED 545 New Equipment in Microbiology Laboratory
RED 546-562 (b) (4) Cetirizine 5mg Tab Process Qualification Protocol
RED 563-577 (b) (4) Cetirizine 10mg Tab Process Qualification Protocol

RED 578-579 Process Flow – Cetirizine 5mg tab
RED 580-581 Process Flow – Cetirizine 10mg tab
RED 582-583 Stability Specification for Cetirizine 5mg tablets
RED 584-585 Stability Specification for Cetirizine 10mg tablets
RED 586-595 SOP (b) (4) re
RED 596-597 Differing Pages from Submission
RED 598-603 InterOffice Memo re: Cleaning Validation Evaluation of Cetirizine
RED 604-609 Cleaning Validation Evaluation – Cetirizine 5mg and 10mg
RED 610-637 Manufacturing Order – Current Batch Card, Cetirizine 5mg tab
RED 638-667 Manufacturing Order – Current Batch Card, Cetirizine 10mg tab
RED 668-669 Scale Up Batch Sequence and Coating Parameters – for both Cetirizine 5mg and 10mg tablets
RED 670-677 Compu-Coat recipe printout for Cetirizine
RED 678-688 Use of RM (b) (4) – May 24/06 Forward
RED 689-690 Recipe Batch Report printout example from the Coating System for product (b) (4)
RED 691 Hold Time Limits specified for Cetirizine
RED 692-730 Deviation Investigation (b) (4)
RED 731-736 06/01-11/30/06 RM (b) (4) Receipt findings – Microbiological testing
RED 737-740 Certificate of Analysis for Perrigo batch (b) (4)
RED 741 Product Recall Document – products (b) (4)
RED 742 Project Profile Document – for Microbiological Contamination Reduction
RED 743 Starch Raw Materials list
RED 744-753 SOP (b) (4)
RED 754-770 Deviation Investigation (b) (4)
RED 771-780 Deviation Investigation (b) (4)
RED 781-797 Deviation Investigation (b) (4)
RED 798-807 SOP (b) (4)
RED 808-812 Process Qualification Protocol, SAN (b) (4)
RED 813-826 SOP (b) (4)
RED 827-828 Coating Solution Manufacturing Order, product (b) (4)
RED 829-832 SOP (b) (4)
RED 833 Microbiological Report, Specification Changes for Limits from (b) (4)
RED 834-835 Raw Material specification, RM (b) (4)
RED 836-839 Cleaning Validation Equipment Specification Sheet – Swab Sites
RED 840-841 Swab Recovery Studies for Stainless Steel
RED 842-843 Swab Recovery Studies for Anodized Aluminum

RED 844-850 SOP (b) (4)

RED 851-853 QC OOS list 2004-2006
RED 854-872 SOP (b) (4)
RED 873-874 2 pages from a metal detection log record (pertaining to (b) (4).

MSM1-3: ANDA and NDA Listing
MSM4-5: NDA Field Alerts List
MSM6: Temporary Change List Suspensions
MSM7-12: SOP (b) (4)
MSM13-14: Revision List for SOP (b) (4) s
MSM15-22: SOP (b) (4)
MSM23: Revision list for SOP (b) (4)
MSM24-26: Temporary Changes SAN (b) (4)
MSM27: Temporary Changes SAN (b) (4)
MSM28: Temporary Change SAN (b) (4)

MSM29-73: Perrigo Quality Notification (b) (4) Berry Suspension 4 oz. dated 3/24/2005 for OOS results for Ibuprofen, Sodium Benzoate, and Butylparaben
MSM74-76: Temporary Change SAN (b) (4)
MSM77: Perrigo Test Method (b) (4) Positive and Negative testing for Pregnancy Test Devices
MSM78: Product release Specifications (b) (4) Pregnancy Test Kits
MSM79: List of Product Run on (b) (4) #2
MSM80-106: Perrigo Quality Notification (b) (4) PCH pregnancy Test 1's (b) (4)) dated 11/02/2005 for material failure to respond to ID test.
MSM107-111: Functional Test Procedure for (b) (4) Semi Finished Product (Pregnancy test kits) from (b) (4) China
MSM112-122: SOP (b) (4)

MSM123: Equipment Cleaning and Use Log for (b) (4) dated

11/03/06 to 11/08/06
MSM124-126: SOP(b) (4)
MSM127-134: Ibuprofen Suspension (b) (4) Stability testing Program
MSM135: Summary of Stability Studies and Data Available for (b) (4) Child Ibuprofen Suspension
MSM136-143: Quarterly Complaint Summary Report dated September 19,2006
MSM144-145: Monthly Complaint Listing dated October 10,2006
MSM146-147: Monthly Complaint Listing August 16,2006
MSM148-149: Monthly Complaint Listing Dated September 19,2006
MSM150-154: Foreign Tablet Prevention Actions
MSM155-161: SOP(b) (4)
MSM162-163: Complaint response for File number 2006-02054 for case number (b) (4)
MSM164-183: Complaint CASE(b) (4) dated Sept 20,2006 for unidentified capsule found in bottle of GNP 81mg aspirin. (Repetitive narrative)

MSM184-196: Complaint Case (b) (4) dated Oct 24,2006 separation of Milk of Magnesia. (No sample requested when available)
MSM197-199: (b) (4) Problem Types and Codes
MSM200-202: SOP(b) (4)
MSM203: Deviation Notification User Group

MSM204-209: Art and Print Request for Labeling changes for Tussin DM Clear Liquid 8Oz for (b) (4) customer
MSM210-221: SOP(b) (4)
MSM222-225: SOP(b) (4)
MSM226-229: SOP(b) (4)
MSM230-235: SOP(b) (4)
MSM236-241: SOP(b) (4)
MSM242-245: SOP(b) (4)
MSM246: Equipment Cleaning and Use log for 100 gal (b) (4)
MSM247-266: SOP(b) (4)
MSM267-289: Bulk manufacturing Order Batch (b) (4)
MSM290: Equipment Cleaning and Use Log for (b) (4) dated 11/05/06 to 11/10/06
MSM291: Equipment Cleaning and Use Log for (b) (4) dated 11/28/06 to 12/02/06

MSM292: Production order for batch (b) (4)
MSM293-294: Perrigo Quality Notification (b) (4) dated 11/29/06 PDT Daytime PE Original 6Hr Liquid 10oz
MSM295–329: batch records for manufacturing batch (b) (4) and packaging Batch (b) (4)
MSM330-331: (b) (4) Cleaning Procedure checklist for batch (b) (4) SAN (b) (4)
MSM332-333: (b) (4) Cleaning Procedure checklist for batch (b) (4) SAN (b) (4)
MSM334-335: (b) (4) Cleaning Procedure Checklist for batch (b) (4) SAN (b) (4)

MSM336-344: Perrigo Quality notification (b) (4) dated 06/08/2006 FM Suspension Infant drops for not properly executing (b) (4) in (b) (4)
MSM345-353: Perrigo Quality Notification (b) (4) dated 05/25/2006 FM Ibuprofen suspension for OOS results for Sodium Benzoate
MSM354-362: Perrigo Quality notification (b) (4) dated 12/02/2005 FM Ibuprofen Suspension for over addition of corn syrup solids
MSM363: Summary of stability Studies and Data for (b) (4) Child Ibuprofen Suspension
MSM364: request for stability waiver product code (b) (4) level AB
MSM365-397: Batch record for (b) (4)
MSM398: Equipment Cleaning and Use Log for 102 dated 10/08/06 to 10/11/06
MSM399-425: Batch records for (b) (4)
MSM426: Equipment Cleaning and Use Log for (b) (4) dated 11/28/06 to 12/03/06
MSM427: Equipment Cleaning and Use log for (b) (4) dated 11/08/06 to 11/28/06
MSM428-446: Perrigo Quality notification (b) (4) dated 10/05/05 Nasal Spray No drip pump liq 1 oz for lose caps found at labeler
MSM447-455: Complaint case Number (b) (4) dated 11/29/06 (b) (4) Pregnancy test
MSM456-463: Complaint case number (b) (4) dated 11/29/06 (b) (4) Pregnancy test

ATTACHMENTS

1 – Preliminary Metal Fragment Investigation Related to Recall of Acetaminophen 500mg Caplets
2 – Initial Summary of Events surrounding Metal Investigation.
3 DQRS Complaint (b) (4) dated 8/8/06
4 DQRS Complaint (b) (4) dated 7/15/06

Patsy J Domingo, Investigator

Rebecca E. Dombrowski, Investigator

Martha Sullivan-Myrick, Investigator